Erythrocyte Iron Incorporation but Not Absorption Is Increased by Intravenous Iron Administration in Erythropoietin-Treated Premature Infants

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ABSTRACT Because critically ill premature infants experience significant iron loss due to phlebotomy and have high iron needs for growth, Fe absorption and incorporation studies are clinically important. A prospective, controlled, randomized, open 21-d study was conducted in infants with birth weight <1300 g and gestational age < 31 wk to assess the efficacy of combining intravenous (IV) sucrose iron (Fe) with erythropoietin (EPO) for increasing Fe absorption, RBC Fe incorporation, and erythropoiesis. Three clinically stable groups were enrolled at 3–4 wk of age: Control, EPO (2100 U EPO/(kg wk)); and IV Fe+ EPO [2 mg IV sucrose Fe/(kg d) plus 2100 U EPO/(kg wk)]. All subjects received 9 mg/(kg d) of oral Fe polymaltose. Subjects were not allowed RBC transfusions. Indicators of iron status and erythropoiesis were assessed before and 18 d after treatment. On d 4, tracer doses of oral polymaltose $^{57}$Fe and IV sucrose $^{57}$Fe were administered, and stool and blood samples were collected for Fe absorption and incorporation determinations. Compared with the Control group, the EPO group demonstrated greater hemoglobin (Hb) concentration and reticulocyte count, but no difference in Fe incorporation. In contrast, the IV Fe+EPO group demonstrated greater total Fe incorporation, Hb concentration, plasma ferritin, and reticulocyte count compared with the Control and EPO groups. Absorption of $^{57}$Fe and nonisotopic polymaltose Fe did not differ among the groups (range: 48–58%, and 41–47%, respectively). We conclude that IV sucrose Fe administered in combination with EPO to very-low-birth weight premature infants significantly increases RBC Fe incorporation and erythropoiesis more than EPO alone, but without increasing iron absorption. 


KEY WORDS: • anemia • iron status • erythropoietin • stable isotope

Very-low-birth weight (VLBW) infants commonly receive one or more RBC transfusions as treatment of anemia. In these infants, anemia is the result of the inability of endogenous RBC production to keep pace with ongoing phlebotomy loss and rapid growth (1). Although treatment with erythropoietin (EPO) and oral iron (oral Fe) stimulates erythropoiesis, the efficacy of EPO in reducing RBC transfusions has fallen short of expectations (2–4), with limited iron availability for sustained erythropoiesis suggested as an explanation (5–7). Support for this is based on efficacy data in normal adults and adults with end-stage renal disease given intravenous iron (IV Fe) after oral Fe supplementation proved ineffective (5,8,9).

Following these studies in adults, 3 studies in premature infants were published in which IV Fe in combination with EPO was administered to prevent anemia (7,10,11). Although the 2 longer studies (3.5–10 wk) did not demonstrate a reduction in transfusions for infants receiving EPO + IV Fe (10,11), one demonstrated an increase in reticulocyte count and hematocrit (7). The third study, our previous report (7), demonstrated increases in the 2 primary outcomes, hemoglobin (Hb) and reticulocyte count among infants who were not allowed to receive RBC transfusions during the relatively brief 18-d treatment period.
The present study extends our previous publication by reporting on the iron metabolism findings. The present study’s objective was to test the hypothesis that EPO administered in combination with IV Fe enhances RBC iron incorporation (Fe incorporation) over that of EPO plus oral iron, or of oral iron alone. To test our hypothesis, we administered isotopic nonradioactive oral $^{57}$Fe and IV $^{58}$Fe to VLBW premature infants already receiving supplemental oral iron and compared Fe incorporation and intestinal Fe absorption in 3 groups of infants, those treated with EPO plus IV sucrose Fe, EPO alone, and oral Fe alone.

SUBJECTS AND METHODS

Following approval by the Ethics Committee of the Medical University of Vienna, Austria, the study was conducted between August 1995 and May 1997. Parents gave written consent.

Study subjects. Characteristics of the participants and the details of the randomization and intervention procedures of this study were reported previously (7). Subject eligibility required clinically stable infants without major abnormalities or major organ disease, <31 wk gestational age, and <1300 g weight at birth. Because of study’s focus on short-term erythropoietic outcomes (i.e., Hb and reticulocyte count), subjects receiving RBC transfusions during treatment were excluded and replaced with the next eligible infant.

Study design. The study was a prospective, controlled, randomized, open label study consisting of a 3-d run-in period followed by an 18-d treatment phase (Fig. 1). Infants were randomly assigned to 1 of 3 treatment groups: Control, EPO, and IV Fe plus EPO (IV Fe+EPO). All subjects received daily oral doses of 9 mg/kg polymaltose Fe (Ferrum Hausmann Syrup, Vifor International) in 4 equal doses immediately before feedings. Infants in the EPO and IV Fe+EPO groups received 900 U/kg of EPO (Janssen-Cilag Pharma) every 3 d. Infants in the IV Fe+EPO group also received 2 mg/kg daily of IV sucrose Fe (Venofer, Vifor International) infused in 0.9% saline over 2 h. All subjects received a daily oral multivitamin preparation (Protovit, Hoffmann-LaRocche) providing ascorbic acid (45 mg/kg), vitamin E (dl-$\alpha$-tocopherol acetate, 25 mg/kg) and folate (50 mg/kg). All but 2 infants were fed their mother’s breast milk supplemented with FM85 Breast Milk Fortifier (Nestle); the other 2 were fed premature formula (BEBa F, Nestle). Venous blood samples were obtained before treatment and on d 0, 11, and 18 (Fig. 1), and 9–12 mo after treatment. Six-day collections of stool in disposable diapers were begun on d 4 after oral $^{57}$Fe dosing.

Isotope preparation and administration. On treatment d 4, all subjects received gravimetrically measured tracer doses of the 2 iron stable isotope preparations, polymaltose $^{57}$Fe and sucrose $^{58}$Fe. Both preparations were compounded by the manufacturer (Vifor International) using procedures identical to those for their commercial products. The isotopically enriched iron was obtained from Dr. Glaser AG (Basel, Switzerland). The $^{57}$Fe and $^{58}$Fe had the following isotopic composition in atom %: $^{54}$Fe < 0.0001%; $^{56}$Fe = 3.6%; $^{57}$Fe = 95.5%; and $^{58}$Fe = 9.9%; and $^{54}$Fe < 0.001%; $^{56}$Fe = 0.45%; $^{57}$Fe = 6.5%; and $^{58}$Fe = 93.05%.

Polymaltose $^{57}$Fe was provided in sealed vials, from which individual infants received ~2.25 mg Fe/kg to replace 1 of their 4 daily oral Fe doses. After $^{57}$Fe dosing, the syringe and tube were flushed 3 times with 1 mL of 0.9% saline, and infants were observed for regurgitation for 15 min. Sterile sucrose $^{58}$Fe (10 g/L) was provided in individual sealed vials containing 15 μL of isotopic solution. The sucrose $^{58}$Fe was diluted with 10 mL of 0.9% saline to a concentration of 15 μg $^{58}$Fe/mL, and ~5.0 mL/kg was infused via peripheral IV over 2 h. For IV Fe+EPO group subjects, the $^{58}$Fe infusion was followed by the subject’s daily 2-h infusion of unlabeled sucrose Fe. For isotopic analysis, blood samples were decomposed in nitric acid in a microwave digestion apparatus (12).

Isotopic analysis and calculations. The $^{58}$Fe/$^{57}$Fe and $^{57}$Fe/$^{56}$Fe isotope ratios (IR) were determined by inductively coupled plasma MS (12). Stool Fe was determined by atomic absorption spectrophotometry (Model 560 Perkin Elmer) followed by ashing (13). The precision of the IR measurements was <0.5% relative SD.

Isotope abundance was calculated from the IRs using an assumed blood volume of 80 mL/kg. Based on isotope abundance, Hb, and body weight, the amount of isotopic Fe incorporated into RBCs was expressed as a percentage of the isotope dose administered (%Inc). The amount of daily iron incorporated in mg/kg (mgInc) was calculated as the product of %Inc and the daily oral or IV Fe dose for individual subjects, i.e., ~9 mg/kg for oral Fe, and ~2 mg/kg IV Fe. Absorption (%Abs) was expressed as a percentage of dose administered not excreted in the 6-d stool collection. Utilization of polymaltose $^{57}$Fe (%Util) was calculated by dividing the percentage of $^{57}$Fe incorporated into RBCs by the percentage of oral $^{57}$Fe absorbed (%Abs) × 100.

Blood analyses. Hematologic variables and plasma ferritin, transferrin, and transferrin receptor concentrations were determined as previously described (7).

Statistical Analyses. Statistical analyses were performed using Statview 5.0 (Abacus Concepts). Natural logarithm values were transformed for nonparametric variables. Among- and within-group comparisons were made by 2-tailed ANOVA or by paired or unpaired t testing as indicated. Variables with significant ANOVA F-values were subjected to post hoc testing using Fisher’s Least Significant Difference test. Associations among study variables were examined using simple linear regression. Results are presented as means ± SEM. The α statistical level of significance applied was $P < 0.05$.

RESULTS

Maternal and infant demographic clinical characteristics and infant hematological outcomes were presented previously (7). The 3 groups did not differ from one another, including in birth weight and gestational age at birth, i.e., Control 1.02 ± 0.08 kg and 27.8 ± 0.7 wk; EPO 0.92 ± 0.07 kg and 27.7 ± 0.6 wk; IV Fe+EPO 1.09 ± 0.07 kg and 28.1 ± 0.5 wk.

Before treatment, laboratory indicators of erythropoiesis and iron status did not differ among the groups. In contrast, a majority of these indicators demonstrated significant differences among groups with respect to their change with treatment (Table 1). Post-treatment change in reticulocyte count and plasma transferrin receptor concentration were greater in the EPO and IV Fe+EPO groups relative to the Control group. For the IV Fe+EPO group, post-treatment change in Hb and plasma ferritin concentrations were greater than in the Control group. The change in plasma transferrin tended to be less in the IV Fe+EPO group than in the other 2 ($P = 0.08$). The change in Hb content of RBCs with treatment did not differ among the groups. Nine to 12 mo after the study, plasma ferritin levels were markedly lower than at the end of treatment, but the concentrations did not differ among the 3 groups (Control: 21 ± 4, n = 7; EPO: 18 ± 2, n = 5; and IV Fe+EPO: 21 ± 2 μg/L, n = 6). Seven infants (39%) had a plasma ferritin concentration <15 μg/L.

FIGURE 1 Study protocol. The duration of and dosing regimens for IV Fe, r-HuEPO oral Fe by infant study group, the iron isotope dosing on d 4, and the times of blood sampling and stool collection are indicated.
Laboratory data in infants at baseline and the change at d 18 of treatment by study group

<table>
<thead>
<tr>
<th></th>
<th>Control, n = 9</th>
<th>EPO, n = 10</th>
<th>IV Fe+EPO, n = 10</th>
<th>ANOVA P Value</th>
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<tr>
<td><strong>Hemoglobin, g/L</strong></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>112 ± 3.2</td>
<td>119 ± 5.8</td>
<td>112 ± 5.2</td>
<td>0.64</td>
</tr>
<tr>
<td>Change</td>
<td>−21 ± 3.4</td>
<td>−14.1 ± 6.9</td>
<td>+3.8 ± 6.8</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Reticulocyte count, × 10⁷/µL</strong></td>
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<tr>
<td>Baseline</td>
<td>82 ± 10</td>
<td>88 ± 12</td>
<td>67 ± 14</td>
<td>0.45</td>
</tr>
<tr>
<td>Change</td>
<td>+36 ± 18</td>
<td>+110 ± 23</td>
<td>+194 ± 24</td>
<td>0.0002</td>
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<tr>
<td><strong>Transferrin receptor, µg/L</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Baseline</td>
<td>2.32 ± 0.41</td>
<td>2.20 ± 0.35</td>
<td>1.76 ± 0.13</td>
<td>0.44</td>
</tr>
<tr>
<td>Change</td>
<td>0.41 ± 0.5</td>
<td>4.45 ± 0.73</td>
<td>5.26 ± 0.81</td>
<td>&lt;0.0001</td>
</tr>
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<td><strong>Plasma transferrin, g/L</strong></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>1.24 ± 0.1</td>
<td>1.23 ± 0.17</td>
<td>1.26 ± 0.11</td>
<td>0.98</td>
</tr>
<tr>
<td>Change</td>
<td>0.15 ± 0.11</td>
<td>0.33 ± 0.23</td>
<td>−0.17 ± 0.06</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Plasma ferritin, µg/L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>310 ± 32</td>
<td>381 ± 73</td>
<td>351 ± 55</td>
<td>0.69</td>
</tr>
<tr>
<td>Change</td>
<td>−131 ± 28</td>
<td>−172 ± 54</td>
<td>371 ± 128</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>RBC Hb content, pg/RBC</strong></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>32.20 ± 0.73</td>
<td>33.16 ± 0.98</td>
<td>33.21 ± 1.10</td>
<td>0.73</td>
</tr>
<tr>
<td>Change</td>
<td>−1.34 ± 0.44</td>
<td>−1.44 ± 0.96</td>
<td>−1.44 ± 0.96</td>
<td>0.99</td>
</tr>
</tbody>
</table>

1 Values are means ± SEM. Superscript letters indicate differences from the Control group: "P < 0.05, "P < 0.01 and differences from the EPO group: "P < 0.05, "P < 0.01.

For the 26 infants successfully completing the 6-d stool collection, Fe absorption did not differ among the groups for either elemental or isotopic Fe (Fig. 2). Total daily mgAbs was 4.9 ± 1.1 mg/kg for the Control group; 4.0 ± 1.1 mg/kg for the EPO group; and 4.1 ± 1.6 mg/kg for the IV Fe+EPO group. When the Fe absorption data for the 3 groups were combined, %Abs was 50.0 ± 3.3%, and the absorptions of elemental Fe and ⁵⁷Fe were directly correlated with one another (r = 0.45, P = 0.02).

RBC incorporation of oral polymaltose ⁵⁷Fe expressed as either the percentage of the dose administered (%Inc) (Table 2) or as the total calculated mg/kg incorporated (mgInc) at 1 wk (data not shown), 2 wk (Fig. 3), and 9–12 mo postisotope dosing did not differ among the groups. Although %Inc of IV ⁵⁷Fe at 1 wk, 2 wk, and 9–12 mo also did not differ among the groups, mgInc was significantly higher in the IV Fe+EPO group (Fig. 3). When the Fe incorporation data for the 3 groups were combined, the %Inc of ⁵⁷Fe and ⁵⁸Fe were directly correlated with one another 2 wk postisotope dosing (r = 0.47, P = 0.014). ⁵⁸Fe %Inc increased by 16.4 ± 4.3% in the interval from 2 wk to 9–12 mo, whereas ⁵⁷Fe %Inc did not increase during this interval.

Iron utilization expressed as the percentage of the absorbed ⁵⁷Fe dose incorporated into RBCs (%Util) tended to increase after treatment in the EPO (P = 0.14) and IV Fe+EPO groups (P = 0.08) (Table 2). This tendency paralleled the significant increases observed in erythropoietic indicators in the EPO-treated groups. ⁵⁷Fe %Abs and ⁵⁷Fe %Inc were not significantly correlated at either 1 or 2 wk after isotope dosing (r = +0.08, P = 0.68; and r = −0.18, P = 0.40, respectively). The Fe %Util for the 3 groups combined was only 6.3 ± 0.8% of the absorbed ⁵⁷Fe dose.

**DISCUSSION**

This is the first iron balance study in premature infants to report on both short- and long-term stable isotope Fe incorporation and absorption after simultaneous administration of oral and IV Fe. This evidence is required for the development of effective strategies to ensure adequate iron availability for normal growth and development in anemic infants (14). In the present study, we demonstrated that IV Fe added to the EPO administered to VLBW infants augments the total Fe incorporation, as determined from the percentage of stable isotopic iron incorporated (%Inc) multiplied by the daily doses (in mg/kg) of oral and IV iron. The observed augmentation of Fe incorporation was paralleled by the change in indicators of erythropoiesis, i.e., Hb, reticulocyte count, and plasma transferrin receptor. The present findings complement our results in a similar, previously studied group of VLBW infants (6). Although the results of the present study are consistent with previous studies in VLBW infants comparing EPO alone with combined treatment with EPO and IV Fe (11,15), previous studies did not include iron kinetic and balance measurements and were confounded by RBC transfusions.
Incorporation of oral and IV iron. Our findings that %Inc of the oral $^{57}$Fe isotope did not differ among the 3 groups does not agree with our previous study in EPO-treated VLBW infants in which a $\geq 200\%$ greater isotopic Fe incorporation was observed in EPO-treated compared with control infants, i.e., 4.4$\pm$1.6\% vs. 2.0$\pm$1.4\%, respectively (6). Differences in the daily oral Fe dosing regimens and formulations may have been responsible, i.e., 9 mg/kg of Fe polymaltose in the present study vs. 6 mg/kg of ferrous sulfate administered previously. Because the daily amount of nonisotopic oral Fe absorbed was $\geq 200\%$ greater than that required for growth in the present study, the portion of the oral $^{57}$Fe directed to stores may have been "buried" beneath the surfeit of unlabeled oral Fe administered 4 times/d (16–18). This speculation is supported by VLBW infant studies indicating that daily isotopic Fe incorporation is inversely associated with the dose of oral Fe administered (6,19–22) (Fig. 4).

Although the IV $^{58}$Fe %Inc at 2 wk did not differ among our 3 infant groups, the mean value for the combined groups was only 35.8$\pm$6.6\% of the dose administered. These data fall between the 17.8$\pm$4.6\% reported by Zlotkin et al. (23) and the 68.3$\pm$2.7\% reported by McDonald et al. in comparable groups of premature infants. When the durations of IV Fe isotope administration of these 2 studies are compared with the present study, the IV infusion time is inversely related to the %Inc, i.e., 8–12 h in Zlotkin et al., 2 h in the present study, and 0.5 h in McDonald et al.

Absorption of oral iron. There were no differences in the $^{57}$Fe absorption of isotopic iron expressed as a percentage of the dose (%Abs) among the study groups, and the combined %Abs for $^{57}$Fe observed for all subjects, i.e., 50$\pm$3\%, is consistent with the 25–50\% Fe absorption measured directly in preterm (6,19–21,24,25) and term infants (13,26). This %Abs is high relative to the $\leq 15\%$ Fe absorption reported for older children and adults (16). Moreover, the high Fe absorption for infants seems paradoxical in the context of high plasma ferritin concentrations, which are indicative of ample iron stores, at birth and during the first months of life. Although this difference in Fe absorption suggests poorly regulated Fe absorption compared with adults, greater Fe absorption may be advantageous for infants in early life when rapid growth is accompanied by increasing iron needs for a rapidly expanding RBC mass and for a central nervous system undergoing profound development change (27,28). Although the mechanism of the high infant Fe absorption observed relative to other studies is uncertain, it could be because $\geq90\%$ of the study infants were breast-fed or because polymaltose-Fe was selected as the oral formulation administered.

Utilization of oral iron. Fe utilization (%Util) calculated as %Inc divided by %Abs did not differ among the groups.

### TABLE 2

Stable iron isotope results in infants at 11 and 18 d and 9–12 mo after iron isotope dosing by study group

<table>
<thead>
<tr>
<th></th>
<th>Control, n = 9</th>
<th>EPO, n = 10</th>
<th>IV Fe + EPO, n = 10</th>
<th>ANOVA</th>
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<tbody>
<tr>
<td>$^{57}$Fe RBC incorporation, % of enteral dose</td>
<td></td>
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<tr>
<td>d 11</td>
<td>1.56$\pm$0.28</td>
<td>2.31$\pm$0.32</td>
<td>2.40$\pm$0.28</td>
<td>0.12</td>
</tr>
<tr>
<td>d 18</td>
<td>2.22$\pm$0.42</td>
<td>2.98$\pm$0.51</td>
<td>2.82$\pm$0.39</td>
<td>0.49</td>
</tr>
<tr>
<td>mo 9–12</td>
<td>3.11$\pm$0.68</td>
<td>4.15$\pm$0.96</td>
<td>2.78$\pm$0.67</td>
<td>0.46</td>
</tr>
<tr>
<td>$^{57}$Fe RBC incorporation, % of IV dose</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d 11</td>
<td>21.6$\pm$2.6</td>
<td>29.6$\pm$4.4</td>
<td>27.8$\pm$4.5</td>
<td>0.35</td>
</tr>
<tr>
<td>d 18</td>
<td>35.8$\pm$5.7</td>
<td>36.9$\pm$4.9</td>
<td>36.8$\pm$6.7</td>
<td>0.99</td>
</tr>
<tr>
<td>mo 9–12</td>
<td>60.4$\pm$6.4</td>
<td>42.8$\pm$6.1</td>
<td>49.6$\pm$11.0</td>
<td>0.34</td>
</tr>
<tr>
<td>$^{57}$Fe RBC utilization, % of enteral dose</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>d 11</td>
<td>2.39$\pm$0.56</td>
<td>5.17$\pm$0.90</td>
<td>5.07$\pm$0.99</td>
<td>0.12</td>
</tr>
<tr>
<td>d 18</td>
<td>3.55$\pm$0.68</td>
<td>6.83$\pm$1.40</td>
<td>7.38$\pm$1.56</td>
<td>0.20</td>
</tr>
</tbody>
</table>

1 Values are means $\pm$ SEM [n, if different].

**FIGURE 3** Iron incorporated (mgInc) from oral and IV Fe in RBC of infants in the study groups at d 18. Values are means $\pm$ SEM, n = 8–10. *Different from the control and EPO groups, P < 0.001.

**FIGURE 4** Isotopic RBC Fe incorporation vs. the daily oral iron dose administered to non-EPO–treated VLBW infants. The data are taken from the literature and from the present study.
although there was a trend toward higher Fe %Util in the EPO-treated groups. What was most striking, however, was the low mean infant Fe %Util of 6.4% 2 wk postdosing for all infants combined. In adult studies in which both Fe absorption and incorporation were measured directly, 80–100% of the iron absorbed was rapidly incorporated, i.e., within 2 wk, into RBCs (16–18). The low %Util observed for infants in the present study in which both %Abs and %Inc were measured directly calls into question the practice of extrapolating adult Fe incorporation data for deriving estimates of Fe absorption in infants (22,23).

Isotopic Fe incorporation 9 to 12 months post-dosing. Our finding of no differences in Fe%Inc among the 3 groups 9–12 mo after isofole administration was anticipated because this interval included several RBC life spans and there was no EPO or IV Fe treatment. The 52 ± 5% IV 58Fe for the combined study groups at 9–12 mo was lower than the 65 ± 8%Inc reported by Garby et al. in 5 term infants 3 mo after IV 59Fe administration at 5–25 d of age (29).

The strikingly low 3.3 ± 0.4% 57Fe %Inc at 9–12 mo is difficult to reconcile in the context of the mean group 6-d 57Fe Abs% of 50 ± 3%. Where did the remaining 46–47% of the absorbed 57Fe go in infants whose plasma ferritin levels, measured simultaneously, had fallen to levels indicative of marginal iron stores? Similarly, an explanation is required for the fact that all of the IV 58Fe was not incorporated into RBCs by 9–12 mo. Iron loss in stool seems one plausible explanation because all infants were in good health after discharge and had little to no laboratory blood loss. This speculation is supported by a report of greater stool iron loss in term infants compared with adults [0.022 vs. 0.014 mg/(kg·d), equivalent to 23 vs. 15%/y of total body iron (d) (4)].

Limitations. The interpretation of the IV 58Fe incorporation mgInc data is difficult because IV sucrose Fe is taken up variably by the reticuloendothelial system (30) and because large amounts of unlabeled oral and IV iron are administered relative to the infants’ daily Fe requirements. Because this was an open study with relatively few study subjects, there is a chance for Type 1 and Type 2 statistical errors, e.g., the trend toward increased Fe %Util in the 2 EPO groups might have reached significance with more subjects. An additional limitation is uncertainty in extrapolating IV sucrose Fe metabolism findings to other parenteral Fe formulations, e.g., to iron dextran which, unlike sucrose Fe, can be administered in parenteral nutrition fluids (31).

In summary, ours is the first iron isotope study in infants in which Fe absorption and concurrent oral and IV Fe incorporation were measured directly. There was a 300–500% greater Fe incorporation (as mgInc) and higher reticulocyte counts and Hb levels compared with VLBW infants treated with EPO plus oral Fe or oral Fe alone. Despite these encouraging results, when the RBC incorporation of IV 58Fe and either the incorporation or utilization of oral 57Fe was expressed as a percentage of the dose administered, we were unable to detect differences in these indicators of iron metabolism among the 3 groups. The greater amount of the calculated Fe incorporated (mgInc) in the Fe+IV Fe group was attributable to IV Fe alone. Contrary to expectation, both isotopic and nonisotopic Fe absorption did not differ among the groups. Thus, although the high Fe absorptions observed among all 3 groups are consistent with previous infant studies, the low percentage of absorbed iron incorporated into RBCs differs markedly from adult data and calls into question the practice of extrapolating Fe absorption based on Fe incorporation in infants (22,23). Future studies in which IV Fe and EPO dosing are modified to achieve more intense and sustained stimulation of erythropoiesis and reductions in RBC transfusions are warranted. Because of iron’s prooxidant activity (32), such studies should evaluate both the safety and efficacy of oral and IV iron.

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