Carbonyl Iron Therapy for Iron Deficiency Anemia

By Victor R. Gordeuk, Gary M. Brittenham, Christine E. McLaren, Margaret A. Hughes, and Louise J. Keating

IRON DEFICIENCY is the most common cause of anemia in the world.1-3 For the past half century the standard therapy for iron deficiency anemia has been ferrous salts.4 Recently, however, Crosby suggested that carbonyl iron may be "an ideal therapeutic agent, effective yet lacking in toxicity."3 Ionic (Fe2+) iron salts such as ferrous sulfate are effective in the correction of iron deficiency anemia, but their use has disadvantages, including the risk of accidental iron poisoning in small children, the occurrence of side effects, and the prolonged duration of treatment required to correct anemia and replenish iron stores. Tablets containing ferrous iron are the second most common cause (after aspirin) of accidental poisoning among small children, leading to as many as 500 hospitalizations and several deaths per year.5 Side effects with a standard dose of ferrous sulfate occur in 10% to 15% of patients when compared to placebo6 and result in difficulty maintaining motivation of patients to comply with therapy. Restoration of hemoglobin to normal with ferrous sulfate requires 3 to 6 months of treatment; replenishment of body iron stores requires therapy for an additional 2 to 4 months.6,4

Elemental uncharged iron powder was used early in this century for treatment of iron deficiency anemia and was nontoxic when compared to ferrous salts.6 However, this elemental iron preparation, which was produced by a hydrogen-reduction process, had poor bioavailability when compared to ferrous salts, possibly due to the relatively large size of the iron particles of about 50 μm and relatively limited reactive surface area.6 Since then the elemental iron preparation known as carbonyl iron powder has been introduced.11 "Carbonyl" does not refer to the composition of the iron particles but rather to the manufacturing process in which the controlled heating of vaporized iron pentacarbonyl leads to the deposition of uncharged, elemental iron as submicroscopic crystals that form microscopic spheres of less than 5 μm in diameter. The preparation is more than 98% pure.12 As a food additive, carbonyl iron has been shown to be well absorbed and utilized for hemoglobin synthesis, both in experimental animals and in humans.13-16 In Sweden, where about half of the fortification iron now used is carbonyl iron, the high bioavailability of this form of iron has been considered one factor contributing to a reduction in iron deficiency.17 Recent studies in rats have clarified the mechanism of absorption of the finely particulate carbonyl iron now available (Huebers et al, unpublished observations). The conversion of particulate carbonyl iron to soluble ionized iron by stomach acid was a prerequisite for absorption and was limited by the rate of gastric acid production. Subsequent uptake by the intestinal mucosa and absorption were similar with equivalent doses of ferrous iron, although absorption of carbonyl iron occurred over a longer interval. In these studies, the bioavailability of carbonyl iron and ferrous iron was similar with doses of 0.2 to 80 mg Fe/kg body weight.

While not previously used pharmacologically, several studies suggest that as a therapeutic agent, carbonyl iron powder may effectively correct iron deficiency anemia yet be considerably less toxic than iron salts. In rats with iron deficiency anemia, carbonyl iron has been used successfully to correct anemia and replace iron stores.12,18 In humans, as in dogs, rabbits, and guinea pigs, the estimated lethal dose of oral ferrous sulfate is about 200 mg Fe/kg body weight.19-21 Human volunteers have taken oral doses of 10,000 mg of carbonyl iron (about 140 mg Fe/kg) "without deleterious effect."5 Formal toxicity studies of carbonyl iron in rats and guinea pigs found that the LD50 (the dose that all animals survive) was 10,000 to 15,000 mg Fe/kg and the lethal dose (LD100) was 50,000 to 60,000 mg Fe/kg.11 These differences in toxicity may be related to differences in the requirements for absorption of iron in the carbonyl and ferrous forms. Fatal amounts of iron may be absorbed through an anatomically intact intestinal mucosa.20 With ferrous sulfate, all the iron in a soluble ionized form is potentially available for absorption. With carbonyl iron, however, only that fraction solubilized by gastric acid is available for absorption; in addition, the rate of solubilization is restricted by the rate of gastric acid production (Huebers et al, unpublished observations).
To determine if carbonyl iron is safe and effective for the treatment of iron deficiency anemia in humans, we carried out studies of dosage, toxicity, and side effects for carbonyl iron in 20 nonanemic volunteers and in 32 patients with iron deficiency anemia.

MATERIALS AND METHODS

The use of carbonyl iron was approved by the Committee on Human Investigation at Cleveland Metropolitan General Hospital. Studies were conducted under the provisions of a claimed investigational exemption for a new drug (IND No. 22289) of the Food and Drug Administration. All subjects participating in the study were advised of the procedures and attendant risks in accordance with our institution’s guidelines and gave informed consent.

Healthy Volunteers

Twenty healthy adult nonanemic volunteers were given orally a reference solution containing 498 mg of ferrous sulfate (100 mg FeSO₄) and 100 mg of ascorbic acid in 0.01 N hydrochloric acid, and at approximately 1-week intervals thereafter, various doses of carbonyl iron powder in gelatin capsules were administered orally. The doses of iron were given after an overnight fast, and the fast was continued for three to four hours after iron ingestion. Ascorbic acid was given along with the ferrous sulfate to permit comparison of our results with previous studies examining the relationship between increase in serum iron concentration and the total amount of iron absorbed. Blood samples were drawn initially and at intervals from 0.5 hour to 24 hours after each dose of ferrous sulfate or carbonyl iron to monitor serum iron, total iron binding capacity (TIBC), percent saturation of TIBC and serum ferritin and to assess liver function as measured by bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase, and renal function as measured by serum creatinine. Five volunteers received carbonyl iron in single incremental doses of 100 mg, 1,000 mg, and 5,000 mg at approximately 1-week intervals; four of these volunteers also received a 10,000 mg dose of carbonyl iron. Blood samples were drawn at 0, 0.5, 1, 2, 3, 4, 5, and 6 hours following the doses of iron. Nineteen volunteers received a 3,000-mg dose of carbonyl iron at approximately 1 week or more after the reference dose of ferrous sulfate, and blood samples were drawn at 0, 3, 6, 12, and 24 hours following the doses of iron. Side effects were monitored on a standardized form that included space to record constipation, diarrhea, heartburn, nausea, abdominal cramps, headache, weakness, and "unpleasant taste." The increase in serum iron was used as an indicator of iron absorption.

Volunteers With Iron Deficiency Anemia

Thirty-two volunteers were recruited from blood donors to the Northern Ohio Red Cross who met the following criteria: (1) menstruating nonpregnant women between the ages of 18 and 40 years and (2) deferral for repeat blood donation because of hemato-crit <38%. They received one of several short-term courses of carbonyl iron powder (shown later in Table 2). Gelatin capsules containing either 500 or 1,000 mg of carbonyl iron were used. Blood samples were drawn at 0, 1, 3, 6, 9, and 12 weeks for determination of free erythrocyte protoporphyrin (FEP), serum ferritin, serum iron, TIBC, percent saturation of TIBC, and complete blood count (CBC) including hemoglobin, mean cellular volume (MCV), white blood cells (WBC), and platelets. In addition, serum bilirubin, SGOT, SGPT, alkaline phosphatase, and creatinine were measured at 0, 1, and 3 weeks. Side effects were recorded on standard forms as described above at weeks 1 and 3 of the study.

Estimation of Iron Absorption. An estimate for the absorption of carbonyl iron was made by calculating the increase in hemoglobin iron and storage iron between weeks 0 and 12 of the study and using the following equation:

\[
\text{Total amount of iron absorbed} = \text{increase in hemoglobin iron} + \text{increase in storage iron}
\]

The increase in hemoglobin iron was calculated using the following equation:

\[
\text{Increase in hemoglobin iron} = \frac{\text{increase in hemoglobin (g/100 mL)}}{3.47 \text{ mg Fe/g hemoglobin}} \times \text{assumed body weight of 60 kg} \times \text{60 mL blood/kg body weight}
\]

The increase in storage iron was calculated by assuming that 1 mg/L of serum ferritin represents approximately 10 mg of storage iron if the serum ferritin is greater than 12 μg/L.23 and that storage iron is absent if the serum ferritin is less than 12 μg/L.24-25 Since at week 0 the serum ferritin was less than 12 μg/L in all but one of our patients, the equation was the following:

\[
\text{Increase in storage iron (mg)} = \frac{\text{serum ferritin (μg/L) at week 12}}{12 \mu g/L} \times 10
\]

In these calculations neither menstrual loss nor dietary absorption of iron was taken into consideration.

Laboratory Methods

Serum iron, TIBC, and percent saturation of TIBC were determined by the methods of the International Committee for Standardization in Hematology (ICSH).26 Serum ferritin was analyzed using FER-IRON immunoradiometric assay kits (Ramco Laboratories, Inc, Houston). FEP was measured with a ZnP model 4000 Hematofluorometer (Environmental Sciences Associates, Inc., Bedford, Mass). CBC was determined with a Coulter Counter Model Z3 or a Coulter Counter Model S-Plus II (Coulter Electronics, Inc, Hialeah, Fla). Serum bilirubin, SGOT, SGPT, alkaline phosphatase, and creatinine were measured by an automated method using the Parallel Analytical System (American Monitor Corp, Indianapolis).

Statistical Methods

Data were analyzed using BMDP computer programs.27 Studies in nonanemic volunteers. For each of five volunteers given incremental doses of carbonyl iron (Fig 1), the mean change in serum iron achieved over three to six hours after each dose of carbonyl iron was examined using a one-way repeated measures analysis of variance. To test the hypotheses that changes in serum iron increased with increasing doses of carbonyl iron, one-sided paired t tests were applied.28 To assure detection of an overall significance level of 0.05, Bonferroni significance levels were used for individual tests.29 The mean changes in serum iron over 24 hours after ingestion of 100 mg of ferrous sulfate and 3,000 mg of carbonyl iron in 19 normal volunteers (Fig 2) were compared using repeated measures analysis of variance followed by two-sided paired t tests. The binomial test29 was used to compare the number of overall gastrointestinal side effects experienced by 18 volunteers following a single dose of ferrous sulfate and carbonyl iron. It was also used to compare the numbers of volunteers experiencing individual side effects after each dose of iron.

Studies in anemic volunteers. Paired t tests were used to compare the mean values for hemoglobin, MCV, FEP, serum ferritin, serum iron, TIBC, and percent saturation of TIBC before and 12
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Fig 1. Change in serum iron over six hours following a reference dose of ferrous sulfate and incremental doses of carbonyl iron. N = 5 for all curves except for 10,000-mg dose of carbonyl iron, N = 4. Statistical significance: 1,000 mg and 100 mg, P = .011; 5,000 mg and 100 mg, P = .0004; 10,000 mg and 100 mg, P = .0003; 5,000 mg and 1,000 mg, P = .0004; 10,000 mg and 1,000 mg, P = .0001.

weeks after carbonyl iron treatment for 32 anemic volunteers (Table 1). Separate one-way analysis of variance procedures followed by pairwise independent sample t tests were used to compare the results of the six treatment regimens shown in Table 2. The Bonferroni multiple comparisons procedure was used to assure detection of an overall significance level of .05. The same methods were used to compare the rates of hemoglobin regeneration for volunteers with three levels of initial hemoglobin concentration. Pearson's r and regression analysis were used to examine the linear relationship between percentage absorption and log cumulative dose of carbonyl iron.11

RESULTS

Healthy Volunteers

Figure 1 shows mean response in serum iron over six hours for incremental doses of carbonyl iron alone and a reference dose of 100 mg of iron as ferrous sulfate plus 100 mg ascorbic acid in five healthy volunteers. It should be noted that addition of ascorbic acid to the dose of ferrous sulfate would be expected to enhance iron absorption and to favor ferrous sulfate as far as the magnitude of the increase in serum iron is concerned. The mean (±SEM) maximal increase (141 ± 25 µg/dL) after the reference dose of ferrous sulfate occurred at three hours. This increment was slightly higher than the mean increase of 110 µg/dL reported by Ekenved et al.,22 which corresponded to a whole body absorption of 8.2 mg iron as determined by whole body counting. With an equivalent dose of 100 mg of carbonyl iron, the rise in serum iron was less abrupt but more sustained, with the maximal increase occurring at the end of the six-hour period of observation. The rise in serum iron following a dose of carbonyl iron increased progressively with incremental doses of 100, 1,000, 5,000, and 10,000 mg of carbonyl iron. However, in no case was the iron-binding capacity of the serum exceeded. Because of the differences in the pattern of absorption with carbonyl iron and with the reference dose of ferrous sulfate, it was not possible to estimate the whole body absorption of the various doses of carbonyl iron from the serum iron studies or to compare the absorption of the two forms of iron directly.

Mean responses in serum iron over 24 hours in 19 healthy volunteers after a reference dose of 100 mg of iron as ferrous sulfate plus 100 mg ascorbic acid and after 3,000 mg of carbonyl iron alone are shown in Fig 2. Mean maximal increases in serum iron were nearly the same following both types of iron. The mean (±SEM) maximal increase (115 ± 13 µg/dL) after ferrous sulfate occurred at three hours, while the mean maximal increase (116 ± 16 µg/dL) after carbonyl iron occurred at six hours. No samples were obtained over the next six-hour period, but no statistically significant differences between the two iron preparations were found (P > .16) either during the first six hours or during the last 12 hours of observation.

Side effects, including gastrointestinal symptoms and an unpleasant taste sensation, were reported by most volunteers both after 100 mg of Fe2+ as ferrous sulfate and after 3,000 mg of carbonyl iron, as depicted in Table 3; these were considered mild by the individuals. Side effect information after carbonyl iron was not available for one of the volunteers. With carbonyl iron the unpleasant taste sensation seemed to be due to eructation. Although overall gastrointestinal (P = .172) and other side effects were not statistically different between the two iron preparations, a significantly greater incidence of diarrhea and of abdominal cramping was seen with carbonyl iron. There was no evidence of hepatic or renal toxicity as measured by individual and mean values for serum bilirubin, SGOT, SGPT, alkaline phosphatase, and creatinine drawn initially and at 24 hours.

Volunteers With Iron Deficiency Anemia

Figure 3 and Table 1 depict response to therapy in all 32 anemic volunteers monitored for a 12-week period after starting a course of carbonyl iron treatment lasting from 7 to 28 days and ranging from 1,000 to 3,000 mg per day in single or divided doses. Mean hemoglobin concentration rose to within normal values by the third week and continued to rise throughout the observation period. Mean MCV and FEP returned to normal. All of these changes were statistically

| Table 1. Short-Term Carbonyl Iron Therapy for Iron Deficiency Anemia |
|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
|                        | Normal                  | Week 0                  | Week 12                  | P                       |
| Hemoglobin (g/dL)      | 12.0-16.0               | 10.8 ± 2                | 12.9 ± 1                 | .0001                   |
| MCV (fL)               | 81.0-99.0               | 80.2 ± 1.2              | 88.3 ± 6                 | .0001                   |
| FEP (µg/dL whole blood)| 10-35                   | 48 ± 3                  | 27 ± 1                   | .0001                   |
| Serum ferritin (µg/L)  | 12-250                  | 5.0 ± 5                 | 15.7 ± 1.8               | .0001                   |
| Serum iron (µg/dL)     | 60-200                  | 71 ± 10                 | 82 ± 6                   | .3652                   |
| TIBC (µg/dL)           | 250-435                 | 417 ± 10                | 356 ± 9                  | .0001                   |
| % Saturation           | 16-50                   | 17 ± 2                  | 23 ± 2                   | .0559                   |

N = 32. Values shown are mean ± SEM.
<table>
<thead>
<tr>
<th>Group</th>
<th>Regimen</th>
<th>N</th>
<th>Cumulative Dose of Carbonyl Iron (mg)</th>
<th>Hemoglobin (g/dL) Week 0</th>
<th>Hemoglobin (g/dL) Week 12</th>
<th>Ferritin (µg/L) Week 0</th>
<th>Ferritin (µg/L) Week 12</th>
<th>Estimated Amount of Iron Absorbed (mg)</th>
<th>Amount of Iron Absorbed per Day (mg)</th>
<th>Estimated Absorption of Carbonyl Iron (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>500–1,000 mg bid to tid for 1–1½ weeks</td>
<td>3</td>
<td>16,000–21,000</td>
<td>10.7 ± .7</td>
<td>13.5 ± .2</td>
<td>3.1 ± .3</td>
<td>14.2 ± 6.1</td>
<td>346 ± 59</td>
<td>47 ± 47</td>
<td>393 ± 48</td>
</tr>
<tr>
<td>II</td>
<td>500 mg tid between meals for 2 weeks</td>
<td>6</td>
<td>21,000</td>
<td>10.1 ± .5</td>
<td>12.7 ± .3</td>
<td>2.8 ± .1</td>
<td>13.7 ± 4.1</td>
<td>336 ± 61</td>
<td>47 ± 30</td>
<td>382 ± 64</td>
</tr>
<tr>
<td>III</td>
<td>1,000 mg bid between meals for 2 weeks</td>
<td>4</td>
<td>28,000</td>
<td>11.1 ± .3</td>
<td>13.0 ± .3</td>
<td>6.6 ± .3</td>
<td>12.8 ± 3.1</td>
<td>235 ± 71</td>
<td>25 ± 25</td>
<td>260 ± 67</td>
</tr>
<tr>
<td>IV</td>
<td>1,000 mg daily between meals for 3 weeks</td>
<td>5</td>
<td>21,000</td>
<td>11.5 ± .1</td>
<td>12.9 ± .2</td>
<td>4.8 ± .8</td>
<td>15.7 ± 3.3</td>
<td>183 ± 56</td>
<td>48 ± 27</td>
<td>231 ± 64</td>
</tr>
<tr>
<td>V</td>
<td>500 mg tid with meals for 3 weeks</td>
<td>8</td>
<td>31,500</td>
<td>10.5 ± .4</td>
<td>12.7 ± .4</td>
<td>4.7 ± 1.0</td>
<td>8.5 ± 2.0</td>
<td>282 ± 36</td>
<td>11 ± 11</td>
<td>293 ± 34</td>
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<tr>
<td>VI</td>
<td>1,000 mg tid with meals for 4 weeks</td>
<td>6</td>
<td>84,000</td>
<td>11.3 ± .2</td>
<td>13.1 ± .2</td>
<td>7.7 ± 1.7</td>
<td>29.8 ± 3.3</td>
<td>232 ± 31</td>
<td>179 ± 33</td>
<td>410 ± 57</td>
</tr>
</tbody>
</table>

Values shown are mean ± SEM.
Statistical comparison of treatment regimens at week 12:
- Hemoglobin: overall P = .783
- Ferritin: overall P = .006; V and VI, P = .0015; other comparisons, P > .05
- Total iron absorbed: overall P = .185
- Iron absorbed per day: overall P = .002; I and IV, P = .003; I and V, P = .0195; I and VI, P = .041; II and IV, P = .003; other comparisons, P > .05
- Carbonyl iron absorption: overall P = .001; I and VI, P = .001; II and VI, P = .001; other comparisons, P > .05
significant. Mean serum iron and mean percent saturation of the TIBC did not change significantly during the study. Mean ± SEM serum ferritin concentration, which was 5.0 ± 5 µg/L initially, rose during carbonyl iron therapy to a peak value of 40.0 ± 4.6 µg/L at week 1 and then declined to a final value of 15.7 ± 2.1 µg/L at week 12, which was significantly greater than the initial concentration. At the end of the study period, hemoglobin was normal (greater than 12.0 g/dL) in 29 of the 32 volunteers, and serum ferritin was greater than 12 µg/L in 14 of the 32 volunteers. Mean serum ferritin in these 14 patients was 26 ± 7 µg/L. Of the 14 patients with normal ferritin at the end of the study, 12 had initial hemoglobin of >11.0 g/dL.

The responses in mean hemoglobin and serum ferritin and estimates of the mean amounts of iron absorbed for each of six different regimens of short-term carbonyl iron therapy used in the anemic volunteers is shown in Table 2. Although the final hemoglobin concentrations were similar among the groups, there were significant differences in the final serum ferritin concentrations. In group VI, which received the largest dose of iron for the longest period of time, serum ferritin was significantly higher than in group V. In group VI hemoglobin was normal and serum ferritin was >12 µg/L in all volunteers after 4 weeks of carbonyl iron therapy.

**Table 3. Side Effects**

<table>
<thead>
<tr>
<th>In Healthy Volunteers Following a Single Dose of Iron (n = 20)</th>
<th>In Anemic Patients During 1 to 4 Weeks of Treatment With Carbonyl Iron (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Volunteers (%)</strong></td>
<td><strong>No. of Volunteers (%)</strong></td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td><strong>Diarrhea</strong></td>
</tr>
<tr>
<td>1 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>0 (0)</td>
<td>8 (44)</td>
</tr>
<tr>
<td>&gt;0.05</td>
<td>&gt;0.04</td>
</tr>
<tr>
<td>9 (28)</td>
<td>24 (75)</td>
</tr>
</tbody>
</table>

Hemoglobin regeneration. The response to carbonyl iron therapy as measured by daily increase in hemoglobin concentration was calculated for each patient. The rate of rise in hemoglobin varied according to the initial hemoglobin concentration but not the treatment protocol. (1) With an initial hemoglobin of 8.9 to 10.0 g/dL, the mean daily increment (±SEM) in hemoglobin was 0.11 ± 0.01 g/dL during the first 3 weeks of the study when carbonyl iron was taken for all or part of this time. (2) With an initial hemoglobin of 10.0 to 11.0 g/dL, the mean daily response in the first 3 weeks was 0.09 ± 0.01 g/dL, and (3) with an initial hemoglobin of 11.0 to 12.0 g/dL, it was 0.04 ± 0.01 g/dL. The hemoglobin regeneration rate for case 3 was significantly lower than for cases 1 (P = .0007) and 2 (P = .0004). As mentioned previously, the mean hemoglobin concentration continued to rise throughout the study period, even following the completion of carbonyl iron therapy. During weeks 6 to 12, when carbonyl iron therapy had been completed for at least 2 weeks, there was a mean daily increase in hemoglobin of 0.01 ± 0.01 g/dL; this increment was seen for all three categories of initial hemoglobin concentration.

Absorption of carbonyl iron. An estimate of the total and daily amount of carbonyl iron absorbed during the study was made for each patient, as shown in Table 2. Estimated total amounts of iron absorbed for the various treatment groups ranged from mean (±SEM) values of 232 ± 64 to 410 ± 57 mg, but there were no statistically significant differences among the six groups. However, when expressed as the amounts of iron absorbed per day, the range was 12 ± 3 to 47 ± 9 mg, and there were significant differences among the groups. Group I, with the shortest duration of therapy, had a greater estimated absorption per day than groups IV, V, and VI, and group II had a greater estimated absorption than group IV. There were also significant differences in estimated percentage absorption of the cumulative dose of carbonyl iron among the groups. Group I and II, which received the smaller cumulative doses, had a greater estimated percent absorption than group VI, which received the largest cumulative dose. Analysis of the estimates of percent absorption for all 32 volunteers revealed a significant negative correlation with the log of the cumulative dose of carbonyl iron (r = −.62; P < .001).

Side effects and toxicity. Side effects, shown in Table 3, were recorded at 1 and 3 weeks of the study in the 32 anemic patients. Gastrointestinal symptoms and an unpleasant taste were reported by a majority of patients. The side effects were considered by the individuals to be mild in most instances, and only three patients considered them severe enough to
warrant discontinuing therapy. In 607 patient-days of therapy with carbonyl iron, there was no evidence for hematologic, hepatic, or renal toxicity as judged by individual and mean values for WBC, platelets, bilirubin, SGOT, SGPT, alkaline phosphatase, and creatinine measured at 0, 1, and 3 weeks.

Cost. Carbonyl iron powder was purchased from GAF Corp (Linden, NJ) at a price of 2 cents per gram. For comparison, the current average price of ferrous sulfate (20% iron) is 35 cents per gram iron, based on manufacturers' listings in the 1985 Drug Topics Red Book for the purchase of 100 capsules or tablets. The cost of the treatment regimens with carbonyl iron in this study ranged from $3.37 to $1.95; standard-dose ferrous sulfate therapy for 4 weeks would have cost, on the average, $1.78. In this comparison, we were unable to take into consideration any additional cost that would result were carbonyl iron to be marketed as a pharmaceutical.

DISCUSSION

Our results suggest that carbonyl iron is safe and effective for the treatment of iron deficiency anemia, is associated with tolerable side effects, and may have a cost comparable to that of ferrous sulfate. We investigated its use as a pharmacologic agent because of studies indicating that carbonyl iron has very low toxicity when compared to standard iron therapy with ferrous salts.5,11,18 In preliminary dosage and toxicity studies, healthy volunteers were given single doses of carbonyl iron ranging from 100 to 10,000 mg with no evidence for toxicity and with mild side effects. It is of note that the 10,000-mg dose of carbonyl iron given to four volunteers is over half the lethal dose of iron as ferrous sulfate (about 14,000 mg in a 70-kg male).19 In five healthy volunteers (Fig 1), the increase in serum iron following a dose of carbonyl iron was less abrupt but more sustained than that from an equivalent dose of ferrous sulfate. Similar results have been obtained in studies of the pattern of absorption of the two forms of iron in rats (Huebers et al, unpublished observations), but no direct studies of the absorption of carbonyl iron in humans are available. Because of the difference in the pattern of absorption between carbonyl iron and ferrous sulfate, relative amounts of iron absorbed with the two iron preparations could not be determined from the data shown in Figs 1 and 2.

A short course of 1 to 4 weeks of carbonyl iron was used to treat patients with mild and moderate iron deficiency anemia. The daily doses of carbonyl iron (1,000 to 3,000 mg in capsules, each containing 500 to 1,000 mg) were 5 to 15 times the usual recommended dose of iron as ferrous sulfate (200 mg in tablets, each containing 65 mg).23 yet side effects were tolerable and there was no evidence of hematologic, hepatic, or renal toxicity. In rats and guinea pigs, the acute lethal dose of carbonyl iron powder lies between an LD50 of 10,000 mg/kg and an LD100 of 60,000 mg/kg.11 If we extrapolate these data to humans, a small child of 10 kg body weight ingesting the largest amount of carbonyl iron prescribed in this study, 84 1-g capsules over 28 days, would have ingested an amount well below the LD50. For comparison, the estimated lethal dose of ferrous iron (200 mg Fe/kg)19 for such a child would be 37 ferrous sulfate tablets (65 mg Fe each), or a 10-day supply for standard adult therapy.

The increases in hemoglobin concentration with carbonyl iron therapy in this study are comparable to those described in previously published studies reporting response to ferrous sulfate,33-36 and to parenteral iron.5,37 It has been shown that the rate of rise in hemoglobin in response to parenteral iron therapy varies inversely with the initial hemoglobin concentration.37 Our results with carbonyl iron also show an inverse relation between the rate of hemoglobin regeneration and the initial hemoglobin concentration similar to that reported in the study with parenteral iron.37 The continued slight mean rise in hemoglobin of .01 g/dL per day following discontinuation of carbonyl iron therapy may have occurred in response to iron that had been absorbed and stored during the period of carbonyl iron therapy, or it may have been due to dietary iron; similar results have been observed both with patients on prolonged ferrous sulfate therapy and with untreated patients responding to dietary iron.36

In the 14 patients who achieved serum ferritin >12 µg/L at the end of 12 weeks of observation, mean serum ferritin was 26 µg/L. This concentration is almost identical to the mean value of 25 µg/L observed in a population of women who were repeat blood donors,38 suggesting that in these patients some iron stores may have been replaced. Further examination of these results shows that while serum ferritin was >12 µg/L in 12 of 19 (63%) patients whose initial hemoglobin was greater than 11.0 g/L, it was above this concentration in only 2 of 13 (15%) patients whose initial hemoglobin was less than 11.0 g/dL. This suggests that although in most patients with mild iron deficiency anemia (hemoglobin 11.0 to 12.0 g/dL) enough iron was absorbed during short-term carbonyl iron therapy to correct anemia and to replace some storage iron, in most patients with moderate anemia (hemoglobin 8.9 to 11.0 g/dL) all of the iron absorbed was ultimately used in erythropoiesis. However, in group VI, which received the greatest amount of carbonyl iron, the final hemoglobin concentration was in the normal range, and the serum ferritin concentration was >12 µg/L in all subjects, suggesting that even a short-term course of carbonyl iron can correct anemia and may at least partially rebuild iron stores in patients with mild iron deficiency anemia. It can be noted parenthetically that in our study, as has been previously reported,39-44 there was a rise in serum ferritin during iron therapy, which apparently did not reflect storage iron (Fig 3). It was for this reason that we used the final serum ferritin values, obtained 56 to 77 days after completion of iron therapy, as the indicator of storage iron. It should also be pointed out that in this study we have not shown that the final hemoglobin concentration, though in the normal range, was the optimal level for the individual patients. It is possible that the hemoglobin concentration continued to rise after 12 weeks (Fig 3) and that some storage iron was used for hemoglobin production after 12 weeks. The 12-week serum ferritin cannot, therefore, be viewed as a definitive measure of storage iron achieved by carbonyl iron therapy in this study.

Side effects occurred in most anemic patients given car-
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bonyl iron in this study, predominantly diarrhea, abdominal cramps, and an unpleasant taste sensation. Although such side effects are a potentially serious drawback to the use of carbonyl iron therapeutically, it should be emphasized that most of the individuals considered them mild and tolerable. In the nonanemic volunteers who received a single dose of ferrous sulfate and a single dose of carbonyl iron that contained a 30-fold greater amount of elemental iron, there were no significant differences in overall gastrointestinal side effects between the preparations, but when abdominal cramping and diarrhea were considered separately, their incidences were significantly more frequent with carbonyl iron. Also, since giving a placebo for iron deficiency anemia is associated with a significant incidence of side effects, defining the true incidence of side effects related to carbonyl iron requires a randomized double-blind trial comparing carbonyl iron, ferrous sulfate, and a placebo. Such a trial is now in progress.

Although the exact mechanism of intestinal absorption of iron is still not known, we believe the evidence from this study suggests that absorption of the doses of carbonyl iron used here proceeds in a controlled physiologic manner. Supporting observations include the following: (1) In healthy volunteers, incremental doses of carbonyl iron led to increasing increments in serum iron following the dose (Fig 1); (2) the iron-binding capacity of the serum was not exceeded even with large doses of up to 10,000 mg of carbonyl iron (Fig 1); (3) following an increase in the serum iron after a dose of carbonyl iron, there was a decline in the serum iron at 12 and 24 hours as seen with ferrous sulfate (Fig 2); and (4) in the anemic patients, intact mucosal selectivity in the absorption of carbonyl iron was suggesting by the declining percent absorption associated with increasing cumulative dose of iron and the length of treatment, as is seen with ferrous sulfate therapy. Although an original observation by Volkheimer described nonphysiologic "persorption" of carbonyl iron particles directly into the portal blood in dogs, the doses he gave (when adjusted for body weight) were approximately 80 times the largest dose given to healthy volunteers and 700 times the largest dose given to anemic patients in our study. Previous studies in our laboratory showed "no evidence of particulate or elemental iron" on histologic and electron microscopic examination of the livers of rats fed with extremely large quantities of carbonyl iron (2.5% wt/wt of the diet) for up to 6 months. Studies in rats using radioactive carbonyl iron have also found no evidence for "persorption" (Heubers et al, unpublished observations).

In this study brief courses of 1 to 4 weeks of carbonyl iron therapy were examined to determine the extent to which anemia could be corrected and storage iron replenished with such short-term therapy. Since an earlier study with animals had shown that a single large oral dose of carbonyl iron corrected iron deficiency anemia and replaced storage iron, we wished to find the largest safe daily therapeutic dose of carbonyl iron with side effects no greater than those associated with ferrous sulfate. In addition, with the 12-week observation period, the short-term therapy allowed us to estimate the amount of iron absorbed as described in Materials and Methods. The mean (±SEM) amount of carbonyl iron absorbed per day for the various treatment groups was estimated to be 12 ± 3 to 47 ± 9 mg (Table 3). These amounts compare favorably with the amount of orally administered iron that the marrow can use for erythropoiesis in mild and moderate iron deficiency anemia, approximately 10 to 20 mg per day, and coincide with the finding that in some of our patients, iron in excess of what was needed for erythropoiesis was absorbed and may have been used to replenish storage iron.

In summary, our results provide evidence that carbonyl iron is a safe, effective, well-tolerated, and inexpensive therapy for iron deficiency anemia. Most important, carbonyl iron may have an advantage when compared to the ferrous salts now in use by decreasing accidental iron poisoning in children. Although there is no direct experience with use of carbonyl iron in children, experience in normal volunteers and in animals suggests that the risk of toxicity and poisoning in children would be greatly reduced when compared to ferrous salts. Patients with mild anemia may correct anemia and rebuild iron stores with even a short course of carbonyl iron, but the optimal dose and duration of therapy for more severe anemia remain to be determined.

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Carbonyl iron therapy for iron deficiency anemia

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