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Effect of Oral Iron Therapy on the Upper Gastrointestinal Tract
A Prospective Evaluation

LOREN A. LAINE, MD, EDWARD BENTLEY, MD, and PARA CHANDRASOMA, MD

This study assesses the effect of oral iron therapy on the upper gastrointestinal tract and fecal occult blood testing. Fourteen healthy volunteers completed a checklist of gastrointestinal symptoms, underwent endoscopy and biopsy of the stomach and duodenum, and supplied a fresh stool sample for Hemoccult and HemoQuant testing. They then took ferrous sulfate 325 mg per os *tid for two weeks and had the same evaluation repeated. Gastrointestinal symptoms were rated by the patients on a scale of 0–3, endoscopic findings were numerically scored (0–4), and the biopsies were graded blindly. Thirteen other healthy volunteers took ferrous sulfate 325 mg* per os *tid for one week and had Hemoccult testing of stool at days 0 and 7. All subjects developed dark stools, and significant nausea and diarrhea were noted (0.1 ± 0.1 to 0.9 ± 0.3, $P < 0.05$ for both symptoms). Only 1/27 had a questionably trace-positive Hemoccult test (two observers disagreed) and no significant difference was seen in HemoQuant testing (1.4 ± 0.5 to 1.8 ± 0.7 mg Hb/g). A significant increase was seen in endoscopic abnormalities in the stomach (0.1 ± 0.1 to 1.5 ± 0.3, $P = 0.003$), consisting of erythema, small areas of subepithelial hemorrhage, and, in two subjects, erosions. Biopsies showed no significant change after iron therapy. We conclude that (1) oral ferrous sulfate rarely causes Hemoccult-positive stools, and patients with positive Hemoccult tests on iron therapy require further evaluation; and (2) oral iron may cause mild endoscopic abnormalities in the stomach which are of uncertain clinical significance.*

KEY WORDS: positive tests for occult blood in stools; iron therapy; iron-induced injury to gastric mucosa.

Acute iron poisoning is a common form of childhood toxic ingestion and has been the subject of numerous reports and reviews (1–3). Iron is said to have a direct corrosive action on gut mucosa and children with iron intoxication may present with symptoms of vomiting, diarrhea, and gastrointestinal bleeding (1). Although the therapeutic administration of oral iron also is associated with gastrointestinal symptoms, the effect of oral iron therapy on the gastrointestinal tract of man has not been well studied.

Iron therapy also has been implicated as a cause of false-positive fecal occult blood testing. Lifton and Kreiser (4) reported that Hemoccult (Smith-Kline Diagnostics, Inc., Sunnyvale, California) testing was positive in 65% of stool samples provided by 10 healthy volunteers taking ferrous sul-

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From the Department of Medicine and Pathology, LAC-USC Medical Center–USC School of Medicine, Los Angeles, California.

Address for reprint requests: Dr. Loren A. Laine, Department of Medicine, USC School of Medicine, 2025 Zonal Avenue, Los Angeles, California 90033.

fate for one week. These were assumed to be false-positive reactions, although no quantification of fecal blood loss was done.

We have performed a prospective evaluation in healthy volunteers of the effects of oral ferrous sulfate therapy on gastrointestinal symptoms, endoscopic and histologic findings in the upper gastrointestinal tract, stool Hemoccult testing, and fecal blood loss.

MATERIALS AND METHODS

Fourteen healthy volunteers [13 females, 1 male; mean age 29 years (range 24–48 years)] were studied. None had a history of gastrointestinal bleeding, gastrointestinal diseases, previous gastrointestinal tract surgery, or bleeding disorders. Alcohol, aspirin, nonsteroidal antiinflammatory drugs, and vitamin C were proscribed beginning one week prior to entry into the study. No dietary restrictions were imposed.

Before starting iron therapy, the subjects completed a checklist of gastrointestinal symptoms present over the preceding two weeks. Symptoms included heartburn, nausea, vomiting, abdominal pain, diarrhea, constipation, and dark stools and were rated on a scale of 0–3 (0: absent; 1: mild, not affecting daily routine; 2: moderate, still able to perform normal activities; 3: severe, unable to properly perform daily activities). The subjects also provided a stool sample for Hemoccult II slide testing and for quantification of fecal blood loss by HemoQuant (5, 6) (SmithKline Bio-Science Laboratories, Van Nuys, California). Normal fecal blood loss is considered <3 mg Hb/g stool.

On the same day a pretreatment upper endoscopy was performed (GIF-XQ upper endoscope, Olympus Corporation of America, New Hyde Park, New York) and pinch biopsies were taken from the gastric body, antrum, and duodenum (random biopsies were done unless an area of abnormality was noted). Two observers independently scored the endoscopic findings on a scale of 0–4 (0: normal; 1: erythema; 2: 1–4 areas of subepithelial hemorrhage; 3: 5–10 areas of subepithelial hemorrhage and/or 1–2 erosions; 4: >10 areas of subepithelial hemorrhage and/or >2 erosions and/or an ulcer). The volunteers were given a bottle containing 45 tablets of ferrous sulfate, 325 mg, and told to take the medication three times a day (before meals) for two weeks beginning immediately.

At one and two weeks another symptom checklist was completed. At two weeks stool was collected again for Hemoccult and HemoQuant testing, and repeat upper endoscopy and biopsies were performed (subjects had taken a tablet within 4 hr of the endoscopy). A pill count also was done. All stools were Hemoccult-tested within 12 hr of collection. Stools were tested both dry and rehydrated and scored independently by two observers. Development of blue color within 60 sec was interpreted as a positive test (as per manufacturer's instructions).

All biopsies (formalin-fixed, paraffin-embedded, and stained with hematoxylin and eosin) were read by a single pathologist who was blinded with regard to clinical information. Biopsies were rated on a scale of 0–3 (0 = absent; 1 = mild; 2 = moderate; 3 = severe) for each of the following characteristics: acute inflammation, chronic inflammation, mucosal hemorrhage, mucosal edema, mucosal congestion, epithelial atypia, erosions, and metaplasia. Additionally, the overall degree of biopsy abnormality was graded on a scale of 0–10 (0 = no change; 1–3 = mild change; 4–7 = moderate change; 8–10 = severe change).

In a separate portion of the study, 13 healthy volunteers [12 males, 1 female; mean age 33 years (range 23–50 years)] provided a stool sample for Hemoccult testing and took ferrous sulfate 325 mg *per os* tid for one week. At the end of a week a pill count was done and another stool sample was provided for Hemoccult testing. This portion of the study was done to reproduce the one-week period of ferrous sulfate ingestion in the study of Lifton and Kreiser (4).

Results have been expressed as mean ± SE. Comparisons were made in paired fashion between the results for each subject at the initial evaluation and after two weeks of iron ingestion. Statistical analyses were done using the Wilcoxon signed ranks test (the sign test was substituted in three comparisons in which the Wilcoxon test could not be used). Linear regression analysis was done comparing endoscopic scores with the symptom scores after iron ingestion. A $P < 0.05$ was accepted as significant.

This study was approved by the Research Committee of the Los Angeles County–University of Southern California Medical Center, and all participants signed a written informed consent form.

RESULTS

Table 1 lists the ages and pill counts of the study participants and the results before and after iron therapy of endoscopic and histologic examination and Hemoccult and HemoQuant testing. The 14 subjects took an average of 2.5 ± 0.1 tablets per day (the 13 other volunteers undergoing only Hemoccult testing ingested an average of 2.6 ± 0.1 tablets per day). All participants developed dark brown–black stools. Symptoms of nausea and vomiting increased significantly during the period of iron intake when compared to the two weeks prior to treatment (0.1 ± 0.1 to 0.9 ± 0.3, $P < 0.05$ for both symptoms). An increase in abdominal pain (0.3 ± 0.2 to 0.6 ± 0.2) did not reach statistical significance.

The stool samples of all 27 subjects were Hemoccult-negative at entry. After iron treatment only 1/27 stool samples was questionably trace-positive (one observer reported trace-positive and one reported negative). The results of the dry and rehydrated Hemoccult tests were identical in each stool specimen tested. HemoQuant testing did not

TABLE 1. RESULTS BEFORE AND AFTER FERROUS SULFATE TREATMENT IN HEALTHY VOLUNTEERS

Subject No.	Age (years)	Pill count†	Positive hemoccult		HemoQuant (mg Hb/g stool)		Endoscopic score: stomach (0–4)		Histologic score: stomach (0–10)	
			Before	After	Before	After	Before	After	Before	After
1	28	2.6	–	±	0.4	0.4	0	0.5	1	0
2	31	2.9	–	–	0.6	1.2	0	0	2	1
3	26	2.7	–	–	0.2	0.1	0	2	0	1
4	26	2.6	–	–	0.2	4.7	0	3	0	0
5	24	2.7	–	–	0.6	0.4	0	2	0	1
6	35	1.1	–	–	2.0	0.7	0	1	0	0
7	32	2.8	–	–	2.1	10.0	0	2	0	0
8	25	2.6	–	–	0.8	0.4	1	3	0	0
9	32	2.4	–	–	6.0	2.3	0	0	3	3
10	48	1.6	–	–	0.1	0.4	0	1	0	0
11	27	2.5	–	–	1.7	0.3	0	2	0	0
12	25	2.7	–	–	4.1	3.4	0	1	0	0
13	24	3.0	–	–	0.1	0.2	0	1	0	0
14	25	3.0	–	–	0.3	0.5	0	2	0	1
15–27*	33 ± 2	2.6 ± 0.1	–	–						
Total ($\bar{X}$ ± SE)	31 ± 1	2.6 ± 0.1	0/27	1/27	1.4 ± 0.5	1.8 ± 0.7	0.1 ± 0.1‡	1.5 ± 0.3	0.4 ± 0.3	0.5 ± 0.2

*13 volunteers took iron for seven days and underwent only Hemoccult testing ($\bar{X}$ ± SE).
†Number of pills taken per day ($\bar{X}$ ± SE).
‡p = 0.003 for comparison of endoscopic scores before and after iron ingestion.

change significantly after iron treatment (1.4 ± 0.5 to 1.8 ± 0.7 mg Hb/g stool).

Endoscopic examination of the stomach revealed a significant increase in abnormalities after iron therapy (0.1 ± 0.1 to 1.5 ± 0.3, P = 0.003). The abnormalities consisted of erythema in nine subjects, small areas of subepithelial hemorrhage in six subjects, and solitary antral erosions (5 × 2 mm and 9 × 3 mm in dimension) in two subjects. (Three volunteers had both erythema and subepithelial hemorrhage noted and one had erythema, subepithelial hemorrhage, and an erosion). The regions of erythema and subepithelial hemorrhage were distributed equally between the body and antrum. Two of the volunteers developing endoscopic abnormalities [No. 4 (erosion) and No. 7 (subepithelial hemorrhage)], also had elevated levels of fecal blood loss after iron treatment (0.2 to 4.7 mg Hb/g stool in No. 4 and 2.1 to 10.0 mg Hb/g stool in No. 7). No endoscopic abnormalities of the duodenum were noted either before or after iron ingestion.

Linear regression analysis revealed that the correlation coefficient of endoscopy scores vs abdominal pain scores was significant (r = 0.64, P = 0.01). When endoscopic scores were compared to scores for each of the other gastrointestinal symptoms, all correlation coefficients were ≤0.50 (vomiting: r = 0.50, P = 0.07; diarrhea: r = 0.46, P = 0.10; nausea: r = 0.40, P = 0.16).

Histologic examination of the gastric biopsy specimens revealed no significant change after iron therapy in any specific category or in the general assessment score (0.4 ± 0.3 to 0.5 ± 0.2). No correlation was noted between endoscopic and histologic findings. Only two of the 14 volunteers had abnormalities rated ≥2 (mild inflammation before and after iron intake). No differences were seen when biopsies from the body and antrum were analyzed separately, and no differences were present in the duodenal biopsies before and after iron treatment.

DISCUSSION

Oral iron therapy is usually cited as a frequent cause of false-positive Hemoccult testing, and recent reviews have suggested that iron tablets be avoided in patients undergoing Hemoccult testing (7, 8). In addition, the manufacturer's instruction booklet (SmithKline Diagnostics, Inc., Sunnyvale, California; 1985) recommends suspending use of iron preparations before and during Hemoccult testing. These statements are based primarily on a single prospective study by Lifton and Kreiser in which 65% of the stool samples of 10 healthy volunteers taking ferrous sulfate were Hemoccult positive (4). The results of our study differ greatly. Oral ferrous sulfate could not be implicated as a cause of Hemoccult-positive stool—only one of 27 healthy volunteers had a questionably positive Hemoccult test after iron therapy.

Review of the other data available in patients being treated with oral iron does not support a high incidence of false-positive Hemoccult slide tests.

Morris et al (9) examined 37 stool specimens of patients on oral iron therapy with fecal blood loss <2.0 mg Hb/g stool (by ^{51}Cr-labeled erythrocytes) and found that none had a positive Hemoccult test. Ahlquist et al (5) reported a small but significant increase in positive Hemoccult tests in patients on iron therapy (17.4% of 85 patients taking iron had a positive Hemoccult test, while 9.8% of 577 patients not taking iron also had a positive test—despite comparable mean HemoQuant values for the two groups). However, we cannot exclude the possibility of gastrointestinal blood loss, a common indication for iron therapy, in some of the patients of Ahlquist et al since only mean HemoQuant values for each group were provided. And finally, McDonnell and Elta, in a recent abstract (10), reported that no positive Hemoccult tests occurred in 15 healthy volunteers after one week of ferrous sulfate ingestion.

Mean HemoQuant values in the present study were not significantly different before and after iron intake. One subject (No. 9, Table 1), without abnormalities noted at either endoscopy, had an elevated fecal hemoglobin initially which fell to the normal range after iron treatment. Conversely, two other subjects (Nos. 4 and 7) had an elevation of fecal blood loss to abnormal levels and developed endoscopic abnormalities after iron ingestion. Thus, although most subjects on iron therapy have negative Hemoccult tests because they do not have elevated fecal blood loss, microbleeding from the stomach may occur in some patients taking oral iron. However, this minimal degree of blood loss (≤10.0 mg Hb/g stool), originating in the upper gastrointestinal tract, should be an infrequent cause of a positive Hemoccult test for two reasons: (1) The Hemoccult test is quite insensitive to low levels of fecal blood loss (6, 7) [Ahlquist et al found that the Hemoccult test was positive in only 17.9% of stools with HemoQuant values between 6.4 and 12.8 mg Hb/g stool with an even poorer sensitivity for HemoQuant values of 3.0–6.4 mg Hb/g stool (6)]. (2) A portion of hemoglobin is degraded to porphyrin during its transit along the gastrointestinal tract, and this fraction, containing no peroxidase-like activity, is not detected by the Hemoccult test (5, 7). As the proportion of degraded fecal heme increases, Hemoccult positivity decreases (6). If any microbleeding occurs due to iron effects on the stomach or small intestine, the phenomenon of hemoglobin degradation should decrease the likelihood of Hemoccult positivity.

Both the American Cancer Society and the International Workgroup on Colorectal Cancer recommend annual fecal occult blood testing beginning at age 40–50 with further diagnostic work-up in those with a positive test (11). Of the commercial tests available, by far the most widely used and best studied is the Hemoccult [both controlled trials underway to test the value of screening for fecal occult blood employ the Hemoccult test (University of Minnesota and Sloan-Kettering)] (7). For this reason, we chose to study and review the effect of oral iron treatment on the Hemoccult test alone.

Our data, combined with the reports cited earlier (5, 9, 10) strongly support the view that oral iron therapy rarely causes a positive Hemoccult test. Therefore, we recommend that patients with a positive Hemoccult test while on iron therapy undergo further evaluation. The reason for the marked discrepancy between the positive finding of Lifton and Kreiser (4) and the negative findings in our study and the study by McDonnell and Elta (10) is not clear. All three studies were done prospectively in healthy volunteers, and all employed the Hemoccult II slide test. No changes have been made in the Hemoccult II slide test since its introduction in 1977 (7; personal communication, SmithKline Diagnostics, Inc.). Hemoccult tests were read by two separate investigators in the present study and in the study by McDonnell and Elta (10). Lifton and Kreiser, however, make no mention of having independent examiners evaluate their Hemoccult tests. Assessment of the Hemoccult test may be difficult in patients taking iron because of the dark brown–black color of the stool, and this may provide an explanation for the discrepancy in results between the report of Lifton and Kreiser (4) and the other studies cited (present study, 5, 9, 10).

In vitro evaluation may help determine the potential for a false-positive Hemoccult test due to ferrous sulfate ingestion. Lifton and Kreiser found that 300 mg of ferrous sulfate dissolved in 1 liter of water produced a positive Hemoccult test (4). However, a more detailed analysis of the *in vitro* effect of ferrous sulfate on the Hemoccult test has recently been published in abstract form (12). Ferrous sulfate, 300 mg, dissolved in 1 liter of water did give a positive Hemoccult test, and the pH of this solution was 4. The ferrous sulfate solution was then tested at varying pHs: the Hemoccult test was positive at a pH of 5 but was negative at pHs of 6, 7, and 8. Thus, the *in vitro* testing of Lifton and Kreiser did not simulate the pH in normal human stool. When

normal stool pH of ~7 was reproduced, the ferrous sulfate did not cause a positive reaction on the Hemoccult II slide test. Ferric chloride in water causes a positive Hemoccult test without addition of the hydrogen peroxide developer (12). Fe^{3+} in ferrous sulfate solutions may be responsible for the false-positive Hemoccult reaction at pH 4 and 5 *in vitro,* while the negative Hemoccult tests with ferrous sulfate solutions above a pH of 5 may be explained by the decreased availability of Fe^{3+} at higher pHs (12).

Iron's effect on the gastrointestinal tract has been addressed primarily in acute iron poisoning of children. Iron is reported to have a direct corrosive action on the mucosal surface of the gastrointestinal tract in children with acute iron intoxication (3). Gastrointestinal symptoms occurring within 6 hr of iron ingestion include vomiting, diarrhea, abdominal pain, hematemesis, and melena (1). Variable degrees of gastric and small intestinal mucosal necrosis with associated hemorrhage may be present (2, 3). Sloughing of mucosa with extension into the submucosa is seen in more severely involved areas. Small intestinal lesions are located proximally and are described as being similar to gastric lesions but less severe (3). Venous thrombi are also present and rarely may lead to small bowel infarction (3).

D'Arcy and Howard found that oral administration of ferrous salts to dogs produced dose-related changes in the gastrointestinal tract (13). Gross "ulceration and inflammation" of the stomach and duodenum were observed, while microscopic examination revealed epithelial necrosis and submucosal hemorrhage. The degree of injury diminished markedly in the region distal to the proximal duodenum. Ferrous sulfate reportedly caused slight "damage" in some dogs at doses equivalent to four tablets.

Careful study of the upper gastrointestinal tract in patients receiving oral iron therapy has not been performed previously, to the best of our knowledge. We found that two weeks of oral ferrous sulfate ingestion led to mild endoscopic abnormalities without histologic changes. Our subjects served as their own controls and ingested no other substances which might potentially damage the upper gastrointestinal tract during their participation in the study. Endoscopic abnormalities were seen only in the stomach and consisted of erythema, small localized areas of subepithelial hemorrhage, and, in two subjects, solitary antral erosions. No histologic changes were noted, but the correlation between endoscopic findings and microscopic examination of small mucosal pinch biopsies is notoriously poor (14). Although the volunteers had a significant increase in endoscopic abnormalities after iron ingestion, their overall endoscopic exam was considered only minimally abnormal by both endoscopic observers.

It is tempting to speculate that the changes in the stomachs of our subjects taking ferrous sulfate represent an extremely mild form of the iron-induced injury seen with iron poisoning in children and experimental animals. The minimal endoscopic abnormalities noted with therapeutic doses of ferrous sulfate were mild and are of uncertain clinical significance. However, a statistically significant positive correlation was seen between abdominal pain and endoscopic changes after iron ingestion, and positive correlations not quite reaching statistical significance ($P \leq 0.10$) were present on comparison of endoscopic findings with scores for vomiting and diarrhea. Mechanisms other than mucosal injury may contribute to the symptoms reported in patients taking iron. Perhaps iron-induced changes in gastrointestinal motility play a role in producing symptoms.

In summary, this study presents two major points: (1) Oral ferrous sulfate rarely causes Hemoccult-positive stools, and patients with a positive Hemoccult test while on iron therapy require further evaluation. (2) Therapeutic administration of ferrous sulfate may cause mild endoscopic abnormalities in the stomach which are of uncertain clinical significance.

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