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

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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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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