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Role of Gastric Acid in Food Iron Absorption

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Radioiron absorption tests in human volunteers demonstrated a modest but significant 28% reduction in the absorption of dietary nonheme iron from a meal that was preceded by the administration of 300 mg cimetidine. More pronounced decreases of 42% and 65% were observed with 600 and 900 mg cimetidine, respectively. Antacid caused a 52% decrease in iron absorption whereas pentagastrin had no significant effect. Since 300 mg cimetidine reduces gastric acid secretion by 60%–80% but iron absorption by only 28%, it appears that under normal conditions more gastric acid is secreted than is required for optimal iron absorption; absorption falls only when acid secretion is markedly reduced. Cimetidine in the doses currently recommended would not be expected to have a major effect on iron nutrition, although the combination of high doses of cimetidine with antacids would impair nonheme iron absorption significantly.

The diet of human beings contains many forms of food iron. However, iron compounds from very different sources share common properties with respect to availability for absorption when eaten together in a meal. This has led to the concept that iron destined for absorption enters one of two common pools (1). The heme pool, comprising hemoglobin and myoglobin, contains only a small amount of iron that is, nevertheless, well absorbed. The larger nonheme pool contains all the other iron in the meal and, in a Western diet, supplies at least two-thirds of our iron needs (2). Unlike iron in the heme pool, its availability for absorption is very dependent upon meal composition and other factors operating in the lumen of the stomach and upper small bowel.

Gastric acid is considered to be one of the most important luminal factors necessary for optimal nonheme iron absorption. However, previous studies demonstrating an enhancing effect of gastric acid on nonheme iron absorption have been limited for the most part to patients with achlorhydria (3–5). Achlorhydric subjects may have other gastrointestinal abnormalities such as alterations in gastric emptying and histologic changes in the small bowel mucosa (6–8). The introduction of cimetidine, a potent and highly selective inhibitor of gastric acid secretion, enabled us to study the importance of gastric acidity for food iron absorption in normal subjects. In the present report, we examined the effect of cimetidine on nonheme iron absorption and compared the findings with the effects of antacid and pentagastrin.

Methods

Multiple iron absorption tests were performed in 58 normal volunteers, 39 men and 19 women, ranging in age from 18 to 46 yr. To extend our observations across the full spectrum of body iron stores, studies were also performed in 9 patients with idiopathic hemochromatosis. Three of them were iron loaded, while 4 were iron deficient and 2 had normal iron stores because of therapeutic phlebotomy. The volunteers all had normal hematocrit levels with the exception of the 4 iron deficient patients who had values of 33, 37 39, and 40, respectively. Each subject gave written informed consent prior to participation in the study. All procedures were carried out with the approval of the Human Subjects Committee and the Radiation Safety Committee of the University of Kansas Medical Center.

Test meals were fed to fasting subjects between 7 and 9 AM and only water was allowed for a further 4 h. Each meal consisted of a hamburger (113 g beef), french fries (68 g),

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and a vanilla milkshake (150 ml), and contained 820 kcal. The total iron content was 4.8 mg, of which 3.4 mg was nonheme iron. The extrinsic tag method was used to label the nonheme common pool by adding 0.1 mg iron as ^{59}Fe or ^{55}Fe ferric chloride to the milkshake immediately prior to serving. The validity of this method for measuring nonheme food iron absorption in human beings has been established in a large number of studies under a wide variety of conditions (9–12). In most studies, subjects were given two separate iron absorption tests, on days 1 and 15, using meals tagged with 2 μCi ^{59}Fe. Some subjects had two additional absorption test meals, on days 2 and 16, which were labeled with 5 μCi ^{55}Fe.

Blood was drawn on the first day of the study for the measurement of hematocrit, serum ferritin (13), and background radioactivity and again 14 days later to measure incorporated red cell radioactivity. A final blood sample was drawn 2 wk after the last test meal to measure the increase in radioactivity resulting from the test meals given on days 15 and 16. Radioiron content was assayed on duplicate 10-ml samples using a modification of the method of Eakins and Brown (14). In the normal volunteers, the calculation of percentage absorption was based on a blood volume estimated from the sex, height, and weight of the subjects (15,16) and an assumed red cell incorporation for absorbed radioactivity of 80% (17). In the 9 patients with hemochromatosis, absorption of ^{59}Fe was measured by whole body counting (18).

The effect of cimetidine, antacid, and pentagastrin on iron absorption was examined. All subjects tested with cimetidine were given one 300-mg Tagamet tablet (Smith Kline & French) the night before each test meal in addition to the dose given with the meal. In the antacid study subjects were given 15 ml of Gelusil II (Warner/Chilcott, Parke-Davis Division, Morris Plains, N.J.), containing 1.2 g aluminum hydroxide, 1.2 g magnesium hydroxide, and 90 mg simethicone. Peptavlon (Ayerst, New York, N.Y.) was used in the pentagastrin study in doses of 6 μg/kg body wt.

Statistical analysis was performed after log transformation of percentage absorption because of the skewed distribution of iron absorption measurements (19). To compare absorption between any pair of test meals in the same subject, we used paired *t*-tests to determine whether the mean difference in log absorption differed significantly from 0, which is equivalent to testing whether the mean ratio of percentage absorption differed from unity.

Results

The initial study designed to test the effect of inhibiting gastric acid secretion on iron absorption was performed in 28 subjects, 9 of whom were studied on two occasions (Table 1). A 300 mg cimetidine tablet was given 1 h before the meal. Because results in patients with hemochromatosis did not differ from those in normal subjects with respect to the absorption ratio with: without cimetidine, data on all subjects were analyzed together. Iron absorption averaged 5.37% without and 3.86% with cimetidine. This 28% decrease in absorption was highly significant ($p < 0.01$).

The effect of larger doses of cimetidine was examined in a second study in 8 normal subjects (Table 2). Basal absorption averaged 3.72% (meal A). When 600 mg cimetidine was taken 1 h before the meal, absorption fell to 2.17% (meal B) and decreased further to 1.31% when an additional 300 mg was taken 1 h following the meal (meal C). Thus, increases in the dosage of cimetidine caused successively greater degrees of suppression of iron absorption, 42% and 65% respectively (Figure 1); both these results were statistically significant when compared with no cimetidine ($p < 0.05$).

In the third study, the inhibiting effect of cimetidine on iron absorption was compared with that of an antacid in 10 normal subjects (Table 1). Fifteen milliliters of Gelusil II was given 15 min before and 15 min after the test meal. Without antacid, mean absorption averaged 4.35%; it fell significantly to 2.05% with antacid. This 53% decrease in absorption was highly significant ($p < 0.01$).

In a final study, the effect of stimulating gastric acid secretion by giving pentagastrin 20 min before the test meal was evaluated in normal volunteers (Table 1). Iron absorption measured on 31 occasions in 21 normal subjects averaged 2.0% from the meals without pentagastrin and 1.7% from the meals with it. This small difference was not statistically significant.

Table 1. Effect of Cimetidine, Antacid, and Pentagastrin on Nonheme Iron Absorption

Treatment	Number of observations	Serum ferritin[a] (μg/L)	Iron absorption[a]		Absorption ratio[a]
			Without (−)	With (+)	
Cimetidine	37	30 (23.0–40.8)	5.37 (4.38–6.59)	3.86 (3.16–4.72)	0.72 (0.65–0.79)
Antacid	10	55 (45.4–65.7)	4.35 (3.47–5.45)	2.05 (1.50–2.82)	0.47 (0.36–0.61)
Pentagastrin	31	78 (70.6–86.0)	2.00 (1.66–2.42)	1.70 (1.46–1.97)	0.84 (0.75–0.95)

[a] Geometric mean (±1 SE).

Table 2. Effect of Varying Doses of Cimetidine on Nonheme Iron Absorption in Eight Subjects

Serum ferritin (μg/L)	Iron absorption[a] with cimetidine dose of			Absorption ratio[a]	
	None (A)	600 mg (B)	900 mg (C)	B/A	C/A
43 (42.5–43.6)	3.72 (2.18–6.34)	2.17 (1.33–3.54)	1.31 (0.96–1.78)	0.58 (0.5–0.67)	0.35 (0.24–0.5)

[a] Geometric mean (±1 SE)

Discussion

The literature contains convincing evidence that patients with iron deficiency anemia and histamine-fast achlorhydria have a diminished ability to absorb nonheme dietary iron (5,20,21). The defect in absorption can be corrected by the administration of hydrochloric acid or gastric juice from patients with normal gastric acid output (3–5,22) but not with neutralized gastric juice (4,22), suggesting that gastric acid is necessary for optimal nonheme iron absorption.

Previous studies have demonstrated that 300 mg cimetidine reduces gastric acid output in response to food by 60%–80% without a significant effect on other aspects of gastric function such as gastric emptying time (23,24). However, our observations indicate that 300 mg cimetidine taken 1 h before the test meal produced only a modest although significant 28% decrease in nonheme food iron absorption. While this result supports the earlier conclusion that gastric acid is important for nonheme iron absorption, the effect of cimetidine was considerably less than that expected from the described differences in absorption between iron-deficient patients with achlorhydria and those with normal acid secretion (21). Furthermore, we observed a progressive decrease in iron absorption as the dosage of cimetidine was increased and the period of administration extended (Figure 1). When 2 tablets were given prior to the meal as well as a further tablet 1 h after the meal, the decrease was similar to the difference in iron absorption between iron-deficient patients with achlorhydria and those with normal acid secretion. Thus, our results suggest that a considerable reduction in gastric acid output may occur before there is much effect on iron absorption. Nonheme iron absorption is markedly inhibited only when hypochlorhydria is severe and sustained.

Day-to-day variation in iron absorption is known to occur. It seemed possible that this variation could be due to differences in acid output on different days, so that inadequate gastric secretion sometimes limited iron absorption. However, pentagastrin produced no increase in absorption, suggesting that acid output in response to the administered meal was always sufficient to ensure adequate absorption in normal subjects. This findings is in keeping both with our observations on the effects of cimetidine and with previous studies indicating that gastric juice from iron-deficient subjects with normal acid output does not increase iron absorption in normal controls (5).

The results we obtained also demonstrate that cimetidine has only a modest effect on iron absorption in the doses usually recommended for treating peptic ulcer disease. It is unlikely that most patients treated with the drug will have significant changes in body iron stores. However, patients treated vigorously with high doses of cimetidine in combination

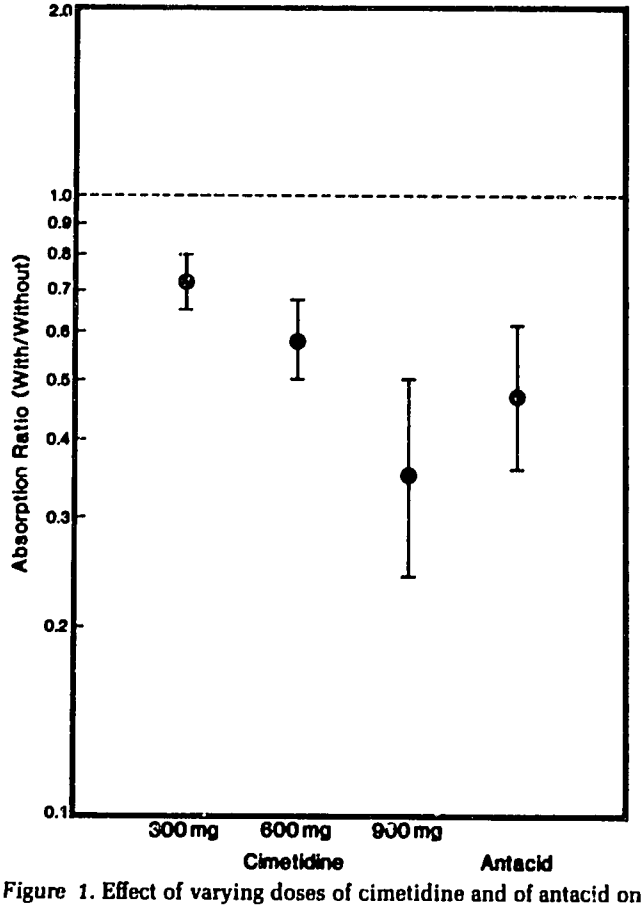

Figure 1. Effect of varying doses of cimetidine and of antacid on nonheme iron absorption. Geometric mean and ±1 SE are shown.

with antacids undoubtedly have a handicap in absorbing dietary nonheme iron. Nevertheless, it is generally agreed that the degree of latent blood loss from the gastrointestinal tract is a more important determinant of iron status than is the nature of the antacid regimen used in most patients with acid peptic disease.

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