

Efficacy of weekly compared with daily iron supplementation¹⁻³

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ABSTRACT A reduction in the frequency of iron supplement administration to once or twice weekly is being widely examined in developing countries on the assumption that the side effects of oral iron will decrease and that the reduction in administered iron will be offset by a lesser inhibition in absorption from iron taken on the previous day. We examined this premise by measuring iron absorption from 50 mg radiolabeled ferrous sulfate in 23 female volunteer subjects divided into two groups. In the first group, a labeled ferrous sulfate supplement was given with water, and in the second group it was given with a rice-based meal. In both groups, absorption was measured in a randomized fashion twice in each subject, once with daily and once with weekly supplementation. Those tested for daily supplementation were given an iron supplement daily for 6 d before testing whereas those tested for weekly supplementation were given no iron for 6 d before testing. When the labeled iron supplement was given with water only, absorption averaged 8.5% with daily and 9.8% with weekly administration compared with 2.3% and 2.6%, respectively, when given with food. The 13% lower absorption observed with daily administration in both groups was not statistically significant ($P > 0.20$). These results indicate that there is no significant absorptive advantage in giving iron less often than once daily. *Am J Clin Nutr* 1995;62:117-20.

KEY WORDS Iron, supplements, absorption, side effects

INTRODUCTION

It is widely believed that iron supplementation of susceptible segments of a population is the most effective method of alleviating iron-deficiency anemia in countries where the prevalence is high. However, long experience with this intervention has shown it to be largely ineffective when used as a public health strategy. The reasons for the limited success of iron supplementation are unclear but poor compliance because of the related gastrointestinal side effects of medicinal iron is commonly cited as an important constraint. Many other factors contribute to the ineffectiveness of iron supplementation in developing countries, eg, limitations in the procurement and distribution of supplies, inadequate public health delivery systems, and lack of awareness by local health workers of the importance of iron-deficiency anemia and of the potential for its elimination by the regular intake of additional iron (1).

One refinement to supplementation programs that has been discussed widely in recent years is the administration of iron less frequently than once daily. This concept is based on studies in

small laboratory animals (2-5) and humans (6-8) that indicate that the administration of oral iron impairs the absorption of a subsequent iron dose. It is argued that by giving iron supplements less often than once daily, any decrease in absorbed iron resulting from a lower total dose will be offset by eliminating the inhibition in absorption from iron given on the previous day. In addition, compliance might be improved by reducing the side effects of iron with less-frequent administration.

More than 20 studies that seek to demonstrate improved response to weekly or twice weekly administration of iron in developing countries are either in progress or are planned (9). These studies are proceeding on the assumption that there is a meaningful inhibitory effect on iron absorption from iron administered on the previous day.

In the present investigation we examined the extent to which daily administration of an iron supplement inhibits the absorption of ferrous sulfate in healthy young women with marginal iron reserves.

SUBJECTS AND METHODS

Subjects

Iron-absorption tests were performed in 23 women between the ages of 21 and 29 y. All considered themselves to be in good health and none had a history of anemia or of disorders known to influence the gastrointestinal absorption of iron. Five of the participants had no iron stores based on a serum ferritin concentration $< 12 \mu\text{g/L}$, and six had reduced stores based on a serum ferritin concentration $< 20 \mu\text{g/L}$. None of the subjects were anemic, as defined by a hematocrit value < 0.38 . Written informed consent was obtained from each volunteer before the investigation, and all experimental procedures were approved by the Human Subjects Committee at the University of Kansas Medical Center.

Study design

The volunteers were divided into two study groups. In the first group, iron absorption was measured from radioactive

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² Supported by NIH grant DK39246.

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Received January 5, 1995.

Accepted for publication March 3, 1995.

ferrous sulfate given with water whereas in the second group the labeled iron was given with a meal. Within each study group the subjects were randomly assigned according to whether, before the first absorption test, the subjects received a daily iron supplement for 6 d (daily supplementation) or received no iron supplement in the previous 6 d (weekly supplementation). Those subjects tested initially for daily iron supplementation took no further iron until they returned 1 wk later for their second absorption measurement (weekly supplementation), whereas those subjects randomly assigned to receive the test dose for weekly supplementation initially were given ferrous sulfate daily for 6 d before returning for their second iron-absorption test. Daily iron supplementation consisted of one ferrous sulfate capsule containing 50 mg elemental Fe (Feosol tablets; Smith-Kline Beecham Corporation, Pittsburgh, PA) taken once daily midway between breakfast and lunch. Subjects were randomly assigned to groups tested initially for the effect of daily or weekly supplementation by drawing their assignment from an envelope.

Iron-absorption measurements

On the first day of the study, blood was drawn from all subjects for measurement of packed cell volume, serum ferritin concentration (10), and background radioactivity. After being randomly assigned to the daily or weekly arm of the study, the subjects returned to the laboratory on day 7 when iron absorption was measured from ferrous sulfate elixir (Smith-Kline Beckman Company, Philadelphia, PA) labeled with ^{55}Fe . All radiolabeled test doses were given between 0700 and 0900 after an overnight fast and nothing further was allowed by mouth for 3 h. Subjects tested initially for daily supplementation then discontinued their daily ferrous sulfate tablet whereas those tested initially for weekly supplementation were given iron daily for the next 6 d. On day 14 of the study, the subjects returned after an overnight fast for a second measurement of iron absorption from ferrous sulfate elixir labeled with ^{59}Fe . Duplicate 10-mL samples of blood were obtained 2 wk later for measurement of incorporated red blood cell radioactivity by using a modification of the method of Eakins and Brown (11). Percentage absorption was calculated on the basis of blood volume estimated from height and weight (12). Red cell incorporation of absorbed radioactivity was assumed to be 80% in all subjects (13).

Ferrous sulfate elixir containing 50 mg elemental Fe was labeled by adding 1.0 mL 0.01 mol HCl/L containing 0.1 mg Fe as either $^{59}\text{FeCl}_3$ or $^{55}\text{FeCl}_3$ to each dose. The amount of radioactivity for each test was 37 kBq ^{59}Fe or 74 kBq ^{55}Fe . In the second study, the labeled ferrous sulfate elixir was sipped at intervals while the subjects were fed a rice-based meal considered typical for many developing countries. The meal was prepared separately for each subject by cooking 15 g cabbage, 15 g cauliflower, 64 g peas, 60 g beans, 14 g vegetable oil, and 30 mL soy sauce for 4 min in a microwave oven and then mixing this combination with 45 g (uncooked weight) steamed, unfortified rice (Riviana Foods Inc, Houston). The meal contained 8.3 g protein, 11.2 g fat, 53 g carbohydrate, and 1444 kJ (345 kcal) as determined from a computerized database (NUTRITION IV software; N-Squared Computing, Salem, OR) and 2.1 mg Fe as determined colorimetrically after acid digestion.

Statistical analysis

Percentage absorption values and absorption ratios were converted to logarithms for statistical analysis and the results were reconverted as antilogarithms to recover the original units (14). Paired *t* tests were used to compare absorption with daily and weekly supplementation by determining whether the mean log absorption ratios differed significantly from zero. Unpaired *t* tests were used to test for differences in absorption ratios between those randomly assigned to weekly or daily supplementation for the first test. The ABSTAT program was used for the statistical analyses (AndersonBell Corp, Parker, CO).

RESULTS

When radiolabeled ferrous sulfate was given with water, the geometric mean absorption when preceded by daily supplementation was 8.49% compared with a slightly higher absorption of 9.75% without prior iron supplementation (Table 1). This 13% difference was not statistically significant. The mean absorption ratio was 0.96 in subjects tested for daily supplementation initially compared with 0.79 in subjects tested for weekly administration first; the difference was not significant.

As expected, absorption with both supplementation regimes was sharply lower when ferrous sulfate was taken with food; absorption averaged 2.28% and 2.62% with daily and weekly supplementation, respectively. The mean absorption ratio for daily/weekly administration was 0.87, identical to that observed when ferrous sulfate was taken without food. The difference was not statistically significant. As in the first study, there was no difference in the absorption ratios between subjects tested initially for daily (0.83) and weekly (0.91) iron supplementation.

When the results in studies with and without food were pooled, the mean ratio of 0.87 for daily/weekly supplementation was still not significant. However, an inverse relation between log serum ferritin and log absorption ratio was nearly significant ($r = -0.410$, $P = 0.052$). This suggests that if daily iron administration does cause any reduction in iron absorption, the effect is less in subjects with low iron stores as measured by the serum ferritin concentration.

DISCUSSION

A relative mucosal block to iron absorption resulting from prior administration of oral iron was first described over half a century ago, based on radioactive iron-absorption tests in iron-depleted dogs (15). This observation was later used as the basis of a theory that intestinal ferritin, which is increased by oral iron administration, controls iron absorption by trapping absorbed iron within the mucosa (16). More recent work indicates that mucosal ferritin functions more as a repository for iron that is not rapidly transferred to the circulation, rather than as a true block in iron absorption (17-19). Although mucosal ferritin does not appear to function as a primary regulator of iron absorption, it is nevertheless closely related to both iron absorption and iron status in animals (20, 21) and in humans (22, 23).

Because of the reduction in iron absorption resulting from prior iron administration, it has been proposed that weekly dosing in iron supplementation programs may approach the effectiveness of daily supplementation. Much of the evidence cited in support of this concept is based on studies in small

TABLE 1
Comparison of iron absorption with daily and weekly administration

Subject	Age	Packed cell volume	Serum ferritin	First dose ¹	Iron absorption		Absorption ratio (daily/weekly)
					Daily	Weekly	
	<i>y</i>	%	$\mu\text{g/L}$		%		
Without food							
1	22	39	5	W	28.18	21.60	1.30
2	21	40	7	D	19.43	15.01	1.29
3	21	43	10	W	12.17	13.58	0.89
4	22	39	15	W	10.96	13.36	0.82
5	22	41	16	W	14.17	10.30	1.37
6	21	43	19	D	7.25	8.35	0.86
7	22	43	20	D	4.80	7.16	0.67
8	22	40	21	D	9.35	7.91	1.18
9	22	41	21	W	5.90	7.93	0.74
10	22	42	24	D	5.56	7.63	0.72
11	25	42	40	D	9.96	8.21	1.21
12	29	41	91	W	1.28	5.21	0.24
\bar{x}^2	23	41	18		8.49	9.75	0.87
- 1 SEM	—	—	15		6.76	8.70	0.76
+ 1 SEM	—	—	23		10.67	10.93	1.00
With food							
1	23	42	8	W	13.45	2.41	5.58
2	27	40	8	D	6.73	10.10	0.66
3	23	44	14	D	3.07	6.76	0.45
4	24	41	14	W	3.50	10.35	0.33
5	22	42	18	D	1.90	1.26	1.50
6	23	45	34	W	1.23	2.26	0.54
7	23	42	36	W	1.11	0.82	1.35
8	24	45	36	D	2.42	2.38	1.01
9	28	43	38	W	0.56	1.02	0.54
10	24	44	61	W	2.15	2.92	0.73
11	24	43	68	D	1.17	1.40	0.83
\bar{x}^2	24	43	24		2.28	2.62	0.87
- 1 SEM	—	—	19		1.74	2.00	0.69
+ 1 SEM	—	—	30		2.98	3.42	1.10

¹ D, daily; W, weekly.

² Geometric mean, except for age and packed cell volume.

laboratory animals (2-5). Caution should be used in extrapolating these findings to human subjects. Recent studies have demonstrated that rats are far less affected by dietary factors known to influence the absorption of nonheme iron in humans (24). It has been demonstrated that dietary iron deprivation in rats produces a significant increase in absorption whereas human subjects are unaffected by prolonged dietary iron deprivation (25). These differences between humans and rats are likely related to a much higher excretion rate from the gastrointestinal tract in rats, which is ≥ 10 -fold higher than in humans (26, 27). The difference may also be related to the large amounts of iron that have been used to demonstrate an inhibitory effect of previously administered iron in rats. Typical studies in rats have used a dose of 4 mg Fe (2, 3), which corresponds to a potentially lethal dose of several grams of iron when extrapolated to humans on a body weight basis. Although it is not surprising that some inhibition of iron absorption can be demonstrated in animal studies using massive doses of iron, the findings have little relevance to programs of iron supplementation in humans.

Certain findings have indicated an inhibiting effect of prior iron in humans. In two such reports, the inhibition was based on a reduction in the postabsorptive rise in serum iron concen-

trations when iron was fed previously. For example, O'Neal-Cutting and Crosby (6) demonstrated that when 30 or 60 mg Fe was given 24 h previously, the postabsorptive rise after a small 10-mg dose of iron was significantly lower (6). A similar effect with different iron doses was reported in a study of the interacting effects of zinc and iron (8). Note, however, that the rise in serum iron after an oral iron dose does not necessarily correlate with absorption. A large number of factors influence the maximum postabsorptive increase in serum iron, eg, gastrointestinal transit time, luminal concentration of iron, rate of entry of iron from the gastrointestinal mucosal cell, and the rate of iron clearance to the erythroid marrow and other body tissues. In general, a relatively poor correlation has been observed between the postabsorptive rise in serum iron and more precise measurements of iron absorption in human subjects (28, 29).

In the only report in which radioiron-absorption tests were used to assess the effect of prior iron administration, a moderate decrease from 35.4% to 29% absorption from a 10-mg dose of iron was observed when 50 mg Fe was given 18 h previously (7). This 18% reduction was statistically significant in 10 adult subjects whereas the 13% decrease in iron absorption in 12

adults observed in the present report was not statistically significant. The magnitude of the effect was small in both studies.

One of the main questions concerning less-frequent administration of iron is whether the amount of absorbed iron can meet the requirements of iron-deficient individuals. When 50 mg Fe was given to iron-replete individuals with food in the present study, 2.3%, or ≈ 1.1 mg Fe, was absorbed daily. If the same amount of iron is given weekly, the iron absorbed would be < 0.2 mg/d. This could be increased somewhat if iron was given twice weekly or if the amount of iron administered weekly was increased; however, the latter would increase the frequency of gastrointestinal side effects and decrease the percentage of absorption. Our results indicate that weekly administration of iron will fall short of the iron required in most situations in which iron supplementation is widely used. In pregnancy, for example, it has been estimated that the average daily iron need during the last two trimesters is ≈ 5 mg (30). Even if iron-deficient women absorb more iron than normal subjects, a daily iron supplement given with food will provide only a small fraction of the needed iron during the latter half of pregnancy.

Another argument in support of less-frequent administration of iron supplements is that the gastrointestinal side effects will be reduced. The most troublesome side effects are those associated with the upper gastrointestinal tract, which occur immediately after oral iron intake, namely nausea, vomiting, and epigastric discomfort. These side effects will also occur with weekly administration, especially if larger amounts of iron are administered less frequently. To the extent that gastrointestinal side effects are believed to influence compliance and thereby the effectiveness of iron supplementation, a more reasonable approach would be to use an iron supplement that does not cause nausea or epigastric discomfort while maintaining comparable or even greater gastrointestinal absorption. One such preparation that has been described recently is a gastric delivery system (GDS) for iron, which retains ferrous sulfate in the stomach while releasing it slowly over several hours (31). If taken with food, which strongly inhibits iron absorption, the iron is retained in the stomach while the bulk of the meal passes on to the small intestine. Field studies have demonstrated a comparable hematological efficacy of GDS as compared with ferrous sulfate administered more frequently (32). The use of this preparation may be preferable to the use of less-intensive iron-supplementation programs that have limited impact on iron-deficient segments of a population. **E**

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