

BIOAVAILABILITY OF IRON SUPPLEMENTS CONSUMED DAILY IS NOT DIFFERENT FROM THAT OF IRON SUPPLEMENTS CONSUMED WEEKLY

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ABSTRACT

Background. Weekly iron supplementation is alleged to prevent iron deficiency anemia as well as daily administration. These studies are based on the hypothesis that prior administration of iron would produce a mucosal block to iron absorption. A weekly dose schedule would allow the renewal of the iron loaded enterocytes, presumably avoiding the iron absorption blockade. **Objectives.** To test the intestinal blockade hypothesis by prior iron administration, and to test the efficacy of weekly vs. daily supplementation schedule on absolute iron absorption. **Methods.** Iron bioavailability was measured in 3 groups of women. In group 1 (n=13) subjects received 60 mg of iron daily for 6 days and in group 2 (n=14) subjects received 120 mg every 7 days for 3 weeks. In both groups the last 240 mg of iron were radioisotopically labeled. In group 3 (n=14) subjects received 60 mg of radioisotopically labeled iron before and after a daily supplementation with 60 mg of unlabeled iron during 6 days. **Results.** Geometric mean iron absorption, standardized to 40% absorption of the reference dose of ferrous ascorbate, with daily (group 1) and weekly (group 2) dosages were 7.7% and 10.9% respectively (unpaired Student t test p = NS). The corresponding values for iron absorption before and after daily iron supplementation (group 3) were 9.7% and 12.5% respectively (paired Student t test p = NS). The total iron absorption of the 240 mg of radioisotopically labeled iron were 18.5 mg and 26.2 mg with daily (group 1) and weekly (group 2) iron supplementation respectively. **Conclusions.** Our results do not support the iron absorption blockade hypothesis. The demonstration that the absolute amount of iron absorbed is similar in both daily and weekly schedules has practical implications for iron supplementation programs.

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INTRODUCTION

Iron deficiency is the most common single nutrient disorder. It is prevalent in most of the developing world and it is probably the only nutritional deficiency of consideration in industrialized countries (1).

Iron deficiency can be prevented by increasing iron intake either by food fortification or supplementation with medicinal iron. In situations in which high rates of iron deficiency prevail or during pregnancy where the very high iron needs of the latter two trimesters are almost impossible to achieve with diet alone, supplementation with medicinal iron constitutes the best method because it can be targeted and produces rapid changes (2).

In recent studies, weekly iron supplementation has been utilized in the prevention of iron deficiency in children, pregnant women and women in childbearing age (3-7). These studies are based on the mucosal block concept that the iron concentration in intestinal mucosal cells in some way regulates the absorption of iron and in the hypothetical presumption that if iron therapy is given intermittently, it would avoid the inhibitory effect of the prior iron dose by allowing mucosal turnover (8-10).

The primary purpose of the study was to test the blockade hypothesis, and a secondary purpose was to consider the efficacy of weekly versus daily supplementation on absolute iron absorption because such data has practical implications in the development and implementation of feasible nationwide supplementation programs. To test the intestinal blockade hypothesis, we compared the absorption of one dose of 60 mg of iron given before and after a daily supplementation with 60 mg of iron during 6 days. To test whether pharmacological doses of iron given in daily or weekly schedule have an effect on iron bioavailability, we compare the average iron absorption of 240 mg of iron administered in 4 consecutive daily doses of 60 mg, with the average iron absorption of 240 mg iron administered in doses of 120 mg per week in the lapse of 2 weeks.

MATERIAL AND METHODS

Subjects: Iron absorption studies were performed in 3 groups of women between the ages of 30 and 50 years. None were pregnant, all used contraceptive intrauterine devices and were in apparent good health. Written, informed consent was obtained from each volunteer before participation in the study. The protocol was reviewed and was in accordance with the standards set by the Institute of Nutrition and Food Technology's Ethics Committee on Human Research; radioactive doses were approved by the Chilean Commission of Nuclear Energy.

Isotope studies: Iron isotopes (^{55}Fe and ^{59}Fe) of high specific activity were used as tracers; both isotopes were iron (III) chlorides as purchased (Du Pont de Nemours, Wilmington, DE). A ferrous sulfate aqueous solution containing 1200 mg/L of elemental iron was labeled extrinsically with tracer amount of $^{55}\text{FeCl}_3$ (Du Pont de Nemours), and a solution containing 60 mg/L of elemental iron, as ferrous sulfate, and 380 mg/L of ascorbic acid was labeled extrinsically with tracer amount of $^{59}\text{FeCl}_3$ (Du Pont de Nemours). The specific activities of the

ferrous sulfate solutions were 0.37 kBq ^{55}Fe /mg elemental iron for studies 1 and 2, and 0.74 kBq ^{55}Fe /mg elemental iron for study 3. The specific activity of the reference dose of ferrous ascorbate was 12.3 kBq ^{59}Fe /mg elemental iron. Isotopes were mixed with the solutions immediately before administration.

The solutions were consumed after an overnight fast, and no food or beverages other than water were permitted during the following 4 hours. For every subject in each study, every iron dose was labeled with radio iron from the same radio iron standard to correct for the radioactivity decay. The amount of solutions ingested was calculated by differential weight of the glasses. For the calculation of total radioactivity ingested, aliquots of the aqueous solutions were counted in sextuplicate as standards.

Measurement of blood radioactivity was performed in duplicate venous samples according to the method of Eakins and Brown (11); they were counted the time necessary to allow <3% counting error. A liquid-scintillation counter (Beckman LS 5000 TD, Beckman Instruments, Fullerton, CA) was used for the double isotope measurements. The percentage of absorption was calculated based on the blood volume estimated from height and weight (12) and assuming an 80% red cell utilization of radio iron (13).

Study 1 (daily schedule): On day 1 the subjects received 3 mg of elemental iron as ferrous ascorbate labeled with 37 kBq of $^{59}\text{FeCl}_3$. On days 12 and 13 of the study 60 mg of unlabeled elemental iron, as ferrous sulfate, was given daily to each subject. Between days 14 and 17 the subjects received a daily dose of 60 mg of iron, as ferrous sulfate, labeled with 22.2 kBq of ^{55}Fe . On day 14, a venous blood was obtained to measure the radioactivity incorporated into erythrocytes from the reference dose. A final venous sample was obtained on day 31 to determine the radioactivity incorporated into erythrocytes from the ferrous sulfate (Figure 1).

Study 2 (weekly schedule): On day 1 the subjects received 3 mg of elemental iron as ferrous ascorbate labeled with 37 kBq of $^{59}\text{FeCl}_3$. On day 7 of the study one dose of 120 mg of unlabeled elemental iron, as ferrous sulfate, was given to each subject. On days 14 and 21, the subjects received a weekly dose of 120 mg of elemental iron, as ferrous sulfate, labeled with 44.4 kBq of ^{55}Fe . On day 14, a venous blood was obtained to measure the radioactivity incorporated into erythrocytes from the reference dose. A final venous sample was obtained on day 34 to determine the radioactivity incorporated into erythrocytes from the ferrous sulfate (Figure 1).

Study 3: On day 1 the subjects received 3 mg of elemental iron as ferrous ascorbate labeled with 37 kBq of $^{59}\text{FeCl}_3$. On day 2 the subjects received one dose of 60 mg of elemental iron, as ferrous sulfate, labeled with 44.4 kBq of ^{55}Fe . Between days 8 and 13 of the study 60 mg of unlabeled elemental iron, as ferrous sulfate, was given daily to each subject. On day 14, a venous blood was obtained to measure the radioactivity incorporated into erythrocytes and the subjects received a second dose of 60 mg of elemental iron, as ferrous sulfate, labeled with 44.4 kBq of ^{55}Fe . On day 20 a second dose of 3 mg of elemental iron as ferrous ascorbate labeled with 37 kBq of $^{59}\text{FeCl}_3$ was given. The time

interval between the last dose of ferrous sulfate and the second dose of ferrous ascorbate was selected to avoid a possible inhibitory effect of the prior iron dose. A final venous sample was obtained on day 34 to determine the increase in red blood cell radioactivity (Figure 1).

In all studies, hemoglobin, mean cell volume, free erythrocyte protoporphyrin, serum iron, total iron binding capacity and serum ferritin were determined in venous blood obtained on day 1, and they were repeated on day 34 in study 3 (14).

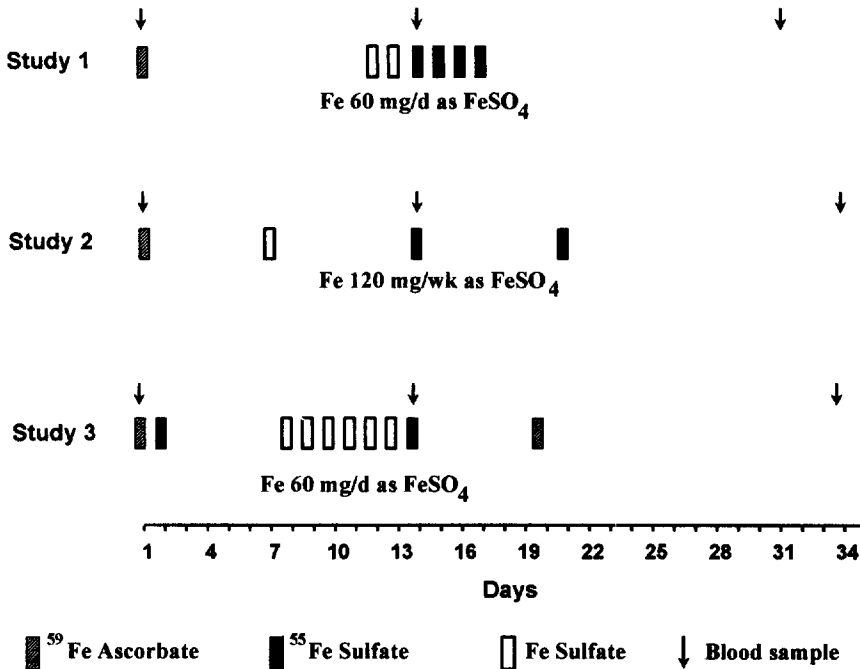


FIG 1. Experimental design. **Study 1:** subjects received 60 mg of elemental iron, as ferrous sulfate, for 6 days. **Study 2:** subjects received 120 mg of elemental iron, as ferrous sulfate, every 7 days for 3 weeks. In both studies the last 240 mg of iron were radioisotopically labeled. **Study 3:** subjects received one dose of 60 mg of iron, as ferrous sulfate, radioisotopically labeled before and after a daily supplementation with 60 mg of unlabeled elemental iron, as ferrous sulfate, during 6 days.

For comparative studies of iron bioavailability, the absorption of 3 mg of elemental iron as ferrous ascorbate is used to offset the effect of differences in iron status among individuals (15). For purpose of comparison, all studies currently refer to 40% absorption of the reference dose of ferrous ascorbate. This percentage is used because it corresponds to that which is obtained in borderline iron-deficient populations. In studies 1 and 2 the absorption of ferrous sulfate was standardized to 40% absorption of the reference dose administered before iron supplementation. In study 3 the absorption of ferrous sulfate administered

before and after iron supplementation was standardized to 40% absorption of the reference dose given before and after iron supplementation respectively.

Because the percentages of iron absorption and serum ferritin concentrations have a skewed distribution, these values were converted to logarithms before performing mean and SD analysis; the results were retransformed to antilogarithms to recover the original units and expressed as geometric means and \pm SD ranges (13). A considerable inter-individual variability in iron metabolism may arise in the premenopausal women studied, due mainly to differences in menstrual iron losses. Because iron absorption from ferrous sulfate and from the reference dose are equally affected by differences in iron status, the inter-individual variability issue was minimized by calculating absorption ratios (ferrous sulfate/reference dose). Statistical analysis included ANOVA and unpaired Student t test for comparison between groups, and paired Student t test for comparison within groups. Paired and unpaired Student t tests were calculated on logarithmically transformed data. Statistical analyses were performed by the program SPSS for Windows, release 6.0, SPSS, Chicago, IL.

RESULTS

One subject of the study 1 (Table 1) and two of the study 3 (Table 3) were anemic. (Hb <120 g/L). Iron depleted stores (serum ferritin <12 ug/L) was found in 3, 6 and 5 subjects of the studies 1, 2 and 3 respectively (Tables 1, 2 and 3).

There were no difference in iron status indicators among the three groups of subjects at the beginning of the study (ANOVA $p > 0.05$). In study 3 there were statistically significant differences, before and after daily supplementation with 60 mg of iron during 6 days, in transferrin saturation [$18.2 \pm 8.9\%$ vs. $22.2 \pm 8.5\%$, paired Student t test $p = 0.046$] and serum ferritin [14.3 (6.5-31.4) ug/L vs. 20.9 (11.8-37.2) ug/L, paired Student t test $p = 0.0036$].

Study 1 (Table 1). Geometric mean absorption of ferrous sulfate with daily administration of 60 mg of elemental iron during 6 days was 6.4 %, becoming 7.7 % when standardized to 40 % absorption of the reference dose. The total iron absorption of the 240 mg of radioisotopically labeled iron was 18.5 mg.

Study 2 (Table 2). Geometric mean absorption of ferrous sulfate with weekly administration of 120 mg of elemental iron during 3 weeks was 7.4 %, becoming 10.9 % when standardized to 40% absorption of the reference dose. The total iron absorption of the 240 mg of radioisotopically labeled iron was 26.2 mg.

Study 1 vs. study 2 (Tables 1 and 2). Ratios of ferrous sulfate/ferrous ascorbate absorption with daily and weekly administration were 0.19 and 0.27 respectively (unpaired Student t test $t=1.953$, $p=0.06$).

TABLE 1
Iron Absorption by Women of 60 mg of Elemental Iron, as Ferrous Sulfate, Given Daily for 4 Days*

Subj.	Age (y)	Hb (g/L)	Sat (%)	FEP ($\mu\text{mol/L}$ RBC)	Serum Ferritin ($\mu\text{g/L}$)	Iron absorption (%)		Ratio A/B
						Ferrous Sulfate ^{55}Fe (A)	Ferrous Ascorbate ^{59}Fe (B)	
1	48	115	13.6	2.17	3.2	27.5	89.6	0.31
2	50	154	24.1	1.42	29.3	2.5	8.1	0.31
3	46	140	21.4	1.36	24.4	6.4	56.5	0.11
4	45	122	25.7	1.01	24.5	5.0	23.8	0.21
5	41	136	15.6	0.81	11.3	8.2	53.9	0.15
6	37	136	21.3	2.33	13.7	7.0	47.2	0.15
7	47	144	18.7	1.26	89.8	6.2	24.6	0.25
8	37	153	15.9	0.86	12.7	8.0	68.3	0.12
9	48	146	25.6	0.81	94.2	4.1	19.3	0.21
10	42	143	23.3	1.31	40.5	5.0	27.4	0.18
11	33	142	11.9	1.52	41.0	4.5	30.7	0.15
12	50	156	14.9	1.11	76.6	6.9	16.5	0.42
13	40	124	11.2	1.42	4.8	8.2	55.8	0.15
Mean	43.4	139	18.7	1.34	23.2 *	6.4 *	33.2 *	0.19 *
SD	5.9	11	5.1	0.40	8.8-61.0	3.7-11.1	15.7-70.5	0.12-0.31

*Abbreviations used: Hb, hemoglobin; Sat, transferrin saturation; FEP, free erythrocyte protoporphyrin

* Because of logarithmic transformation, geometric mean and range ± 1 SD are shown.

TABLE 2

Iron Absorption by Women of 120 mg of Elemental Iron, as Ferrous Sulfate, Given Weekly for 2 Weeks*

Subj.	Age (y)	Hb (g/L)	Sat (%)	FEP ($\mu\text{mol/L}$ RBC)	Serum Ferritin ($\mu\text{g/L}$)	Iron absorption (%)		Ratio A/B
						Ferrous Sulfate ^{55}Fe (A)	Ferrous Ascorbate ^{59}Fe (B)	
1	36	129	31.4	1.01	32.1	7.1	24.0	0.30
2	50	141	24.5	1.36	39.8	5.0	12.4	0.40
3	43	121	26.1	1.52	3.6	8.3	49.3	0.17
4	50	143	23.0	0.86	39.0	6.4	7.9	0.81
5	41	138	23.0	1.11	9.8	7.1	47.4	0.15
6	33	144	22.5	1.22	21.4	8.8	43.3	0.20
7	45	132	23.7	1.21	10.2	17.3	73.2	0.24
8	31	147	25.2	0.86	44.5	4.1	9.1	0.45
9	45	120	13.9	1.47	6.0	22.8	83.6	0.27
10	46	125	20.5	1.52	11.6	11.6	46.3	0.25
11	45	155	21.2	1.06	42.5	4.5	10.5	0.43
12	35	134	20.9	1.97	8.7	9.9	77.6	0.13
13	50	141	30.3	0.66	78.0	2.8	12.8	0.22
14	35	148	24.9	0.96	55.9	4.9	17.6	0.28
Mean	41.8	137	23.7	1.20	20.2 *	7.4 *	27.1 *	0.27 *
SD	6.4	10	4.1	0.33	8.1-50.3	4.3-12.7	11.9-61.7	0.17-0.44

*Abbreviations used: Hb, hemoglobin; Sat, transferrin saturation; FEP, free erythrocyte protoporphyrin

* Because of logarithmic transformation, geometric mean and range ± 1 SD are shown.

TABLE 3

Iron Absorption of One Dose of 60 mg of Elemental Iron, as Ferrous Sulfate, Given Before and After a Daily Supplementation with 60 mg of Elemental Iron During 6 Days*

Subject	Age (y)	Hb (g/L)	Sat (%)	FEP (µmol/L RBC)	Serum Ferritin (µg/L)	Iron Absorption (%)							
						Before				After			
						⁵⁵ Fe (A) **	Ferrous Sulfate ⁵⁵ Fe (B) **	Ferrous Ascorbate ⁵⁵ Fe (C) **	Ferrous Sulfate ⁵⁵ Fe (D) **	Ferrous Ascorbate ⁵⁵ Fe (E) **	A/B **	C/D **	
1	39	122	11.8	1.47	5.0	16.8	79.4	16.3	89.4	29.7	0.21	0.18	
2	35	132	21.9	0.96	14.8	5.6	40.0	5.3	29.7	29.7	0.14	0.18	
3	29	151	23.1	0.96	21.9	9.2	38.3	11.0	25.0	25.0	0.24	0.44	
4	43	167	25.2	0.86	89.8	3.7	8.8	5.7	19.3	19.3	0.42	0.30	
5	40	93	3.6	2.53	5.0	24.1	92.1	28.6	64.6	64.6	0.26	0.44	
6	28	141	8.3	0.91	24.0	8.4	19.1	10.0	31.6	31.6	0.44	0.32	
7	30	148	17.9	1.97	9.7	14.2	67.2	17.1	45.2	45.2	0.21	0.38	
8	43	132	24.0	0.96	29.3	1.7	2.9	2.0	3.3	3.3	0.59	0.59	
9	28	149	25.5	0.96	14.9	10.7	34.4	8.6	16.8	16.8	0.31	0.51	
10	35	160	35.9	0.81	18.3	4.7	27.6	10.7	37.0	37.0	0.17	0.29	
11	35	147	25.7	1.06	23.4	6.8	63.4	10.1	30.3	30.3	0.11	0.33	
12	35	142	15.5	0.76	12.7	12.4	98.6	17.1	100.0	100.0	0.13	0.17	
13	35	134	11.6	2.02	8.4	19.1	72.1	18.1	98.6	98.6	0.27	0.18	
14	36	93	5.4	3.33	4.5	32.8	102.6	32.6	78.1	78.1	0.32	0.42	
Mean	35.1	137	18.2	1.40	14.3 #	9.4 #	38.6 #	11.2 #	35.8 #	35.8 #	0.24 #	0.31 #	
SD	4.8	21	8.9	0.75	6.5-31.4	4.4-20.2	14.4-103.2	5.6-22.5	14.9-86.1	14.9-86.1	0.15-0.39	0.21-0.47	

* Abbreviations used: Hb, hemoglobin; Sat, transferrin saturation; FEP, free erythrocyte protoporphyrin

Because of logarithmic transformation, geometric mean and range ± 1 SD are shown.

**Ratio A/B vs. ratio C/D (paired Student t test, p = 0.054); Ferrous sulfate (A) vs. Ferrous sulfate (B) (paired Student t test, p > 0.05); Ferrous Ascorbate (B) vs. Ferrous ascorbate (D) (paired Student t test, p > 0.05)

Study 3 (Table 3). Despite the increase in serum ferritin, following daily administration of 60 mg of iron for 6 days, there was no statistically significant change in ferrous ascorbate absorption before and after iron supplementation (38.6 % and 35.8 % respectively, paired Student t test $p=0.55$). Ratios of ferrous sulfate/ferrous ascorbate absorption before or after 60 mg daily of elemental iron administered during 6 days were 0.24 and 0.31 respectively (paired Student t test, $t=2.117$, $p=0.054$). When iron absorption was standardized to 40 % absorption of the reference dose, the corresponding percentages of absorption of ferrous sulfate were 9.7% and 12.5 % respectively.

DISCUSSION

Studies performed in rats, children and pregnant women appear to show that intermittent administration of medicinal iron every 3 or 7 days is similarly effective as a daily dose in the control of iron deficiency anemia (3-9). Furthermore, a lower incidence of gastrointestinal side effects was observed in children receiving the intermittent iron supplementation schedule (5). Since in the weekly supplementation studies the administration of iron was strictly supervised, there is concern of its effectiveness in large-scale program. Difficulties in medicinal iron supply, access to health services, and poor compliance are the main pitfalls of large-scale iron supplementation programs, mainly in the undeveloped world (16).

The intermittent iron supplementation strategy is based on the old mucosal block theory that iron concentration in the enterocytes regulates the absorption of iron (17-19). The rationale for using an intermittent schedule of iron administration is that the iron blockade produced by a precedent dose of iron could be avoided if the iron supplement is administered on a weekly schedule that allows time for the enterocyte turnover. The mucosal renewal time is 3 days in rats (20) and about 5 to 6 days in humans (21).

Studies performed in rats have demonstrated an inhibitory effect on iron absorption lasting 48 hours after the consumption of an iron enriched diet (8,9). This inhibitory effect disappears at 60 hours, coincidentally with the enterocyte turnover time in the rat. On the other hand, Viteri et al (10), have shown a higher iron retention in rats receiving an iron enriched meal every 3 days than those fed with the iron fortified meal daily. However, it may be unreliable to extrapolate from animals to humans, the ideal should be to select a species that most closely resembles humans in terms of iron metabolism. There is evidence that the use of rats as surrogate for human absorption studies could be inappropriate since both iron absorption and iron turnover are several times higher in the rat than in man and especially because the main dietary factors that influence iron absorption in humans, such as tannins, phytate and meat, do not affect iron absorption in rats (22).

In humans, O'Neill-Cutting and Crosby (23), showed in 18 mildly iron deficient adults a diminished post-absorptive increase in serum iron when the administration of 10 mg of iron was preceded by an iron dose of 30 to 60 mg given 12 to 24 hours before. A similar effect was shown by Solomons et al (24). However, these results are not necessarily representative of a reduced iron absorption.

In a study with stable isotopes performed in 10 non-anemic adults, it was found that the absorption from a 10 mg iron dose that was preceded 24 hours before by a 50 mg iron dose decreased slightly from 35.4 % to 29.0 % (25).

One of the first pieces of evidence of the non existence of the mucosal blockade in humans was provided by Allgood and Brown in 1967 (26). They showed that the non-heme iron concentration in mucosal duodenum biopsies in human subjects was not correlated with iron absorption. Recently, Cook et al (27), in a study carried out in a group of 23 non-anemic women did not demonstrate a significant difference between the absorption of one dose of radioactive iron administered after 6 days of a once daily schedule of iron supplementation and 6 days after once a week iron supplementation. This study has been criticized because most of the subjects were iron sufficient and only 5 of them had iron depletion. Consequently their iron needs were much lower than the requirements from the subjects of the intermittent supplementation studies published (7,28). The prevalence of anemia and iron depletion in the premenopausal women studied by us was 7.3% and 26.8% respectively. This figure is close to the 8.6% of anemia and 27% of iron depletion found in pregnant women, from Santiago Chile, during the first trimester of gestation (29). Our study, in a group of women that included many iron deficient subjects, absorption of iron administered every 7 days was slightly but not significant higher (10.9%) than absorption of iron given daily (7.7%). These results were obtained using 14 and 13 test subjects respectively. Theoretically, using the difference of means and standard deviation within groups that we have obtained and a power of 80%, a statistically significant difference could be attained if 26 subjects per group were tested. Despite these considerations, the higher iron absorption observed with the weekly iron dosing schedule represents only a 29% and 3.2% relative and absolute change in iron absorption respectively. This increase can be considered negligible in terms of its biological significance. Moreover, iron absorption before 6 days of daily iron supplementation was lower than iron absorption after daily iron dosing (9.7% vs. 12.5% respectively, $p=0.054$). This numerical change has the opposite sign that the results expected according to the mucosal block theory. The hypothesis suggested by the mucosal block theory is that iron absorption should be lower after 6 days of daily iron dosing. Thus, our data and that of Cook et al (27) suggest that there is no mucosal block in man during continuous iron supplementation and that there is no significant absorptive advantage in giving iron in a weekly schedule.

In our study we demonstrate that the absolute amount of iron absorbed was similar in a schedule that provided 60 mg of iron daily for 4 days or 120 mg every 7 days for 2 weeks. This finding could have practical implications for iron supplementation programs. However, our study is short term and supplementation is usually implemented on a long term basis. Further research is needed to explain the results obtained in field studies of intermittent iron supplementation where the total iron received is lower in the intermittent regimen and results in iron nutrition are equal to those obtained in daily iron supplementation with larger total iron given.

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