PN-AAQ-796

ABSORPTION OF CONTROLLED-RELEASE IRON

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Reprinted from
CLINICAL PHARMACOLOGY AND
THERAPEUTICS
St. Louis

Vol. 32, No. 4, pp. 531-539, October, 1982

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(Printed in the U.S.A.)

Absorption of controlled-release iron

A multiple-dose double radioiron technic was used to compare absorption of iron administered as a controlled-release (CR) capsule and as an elixir; both formulations contained 50 mg elemental iron as ferrous sulfate. When taken by normal subjects in the fasting state, mean absorption from the elixir and CR capsule averaged 4.92% and 4.38%, which gave a CR capsule:elixir ratio of 0.89. This difference was not significant, but when taken with meals that inhibit absorption of dietary iron by different degrees, absorption of the CR formulation was superior. CR capsule:elixir absorption ratios averaged 1.70 from a meal that is mildly inhibitory and 3.13 from a meal that causes more marked inhibition. It is concluded that CR iron formulations may offer a therapeutic advantage to patients who take oral iron with meals to avoid gastrointestinal side effects.

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Gastrointestinal side effects such as nausea and epigastric discomfort commonly occur in patients on conventional oral iron therapy. Because these symptoms are believed to correlate with a high concentration of administered iron in the gastrointestinal lumen, a common pharmaceutical approach has been to use iron in a form that retards its rate of dissolution. Reports have shown that controlled-release (CR) preparations reduce gastrointestinal side effects,[27, 32, 33, 37] but the use of these formulations has frequently been criticized on the basis that any reduction in gastrointestinal side effects is due to lower solubility and reduced absorption.[13, 15, 19, 25]

The efficacy of CR preparations reported in a number of studies was based either on hemoglobin response in patients with iron-deficiency anemia[21, 22, 29, 30, 32, 34] or radioisotope determinations,[1-4, 7, 18, 30, 31] with conflicting results. These discrepancies may be due to differences in methods of assessing iron availability or differences in the nature of the CR formulation. Our study was undertaken to compare iron absorption from a commercially available CR capsule (Feosol Spansule capsule) of ferrous sulfate with a modified version of a commercially available ferrous sulfate elixir (Feosol elixir).

Methods

Subjects. Three separate iron absorption studies were performed in 19 male and 31 female subjects whose median age was 26 yr (range, 20 to 55 yr). All subjects were in good health and gave no history of recent infection or of disorders known to impair iron absorption from the gastrointestinal tract. None of the sub-

Supported in part by grants from SmithKline Corporation, National Institutes of Health (AM 19011), and contract DSAN-C-0045 from U.S. Agency for International Development

Received for publication May 12, 1982

Accepted for publication June 10, 1982

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0009-9236/82/100531+09500.90/0 © 1982 The C. V. Mosby Co.

Table I. *Composition of standardized meals*

	Weight (gm)	*Energy (kcal)*	*Protein (gm)*	*Iron content (mg)*
Meal A				
Egg McMuffin	132	352	18	3.2
Bran flakes, 40%	28	86	3	1.3
Sugar	5	19	—	—
Milk, 2% lowfat	227	131	10	—
Coffee	170	2	—	0.2
Total	562	590	31	4.7
Meal B				
Hamburger	94	269	23	3.0
Bun w/dressing	70	151	3	2.1
Potatoes, french-fried	69	210	3	0.5
Milkshake, vanilla	145	162	5	0.1
Total	378	792	34	5.7

jects were anemic according to World Health Organization criteria (hematocrit above 36% in women and 39% in men).[38] Iron status was assessed by serum ferritin determinations by the method of Miles et al.[26]

Preparation of labeled dosage forms. A double radioiron technic was used to compare iron absorption from ferrous sulfate given as ^{59}Fe-labeled elixir and as ^{55}Fe-labeled CR capsules. The method used for preparing and analyzing the radiolabeled CR capsule will be reported separately and is described here only briefly. Commercial ferrous sulfate pellets (250 gm) were irradiated with thermal neutrons for 423 hr at 40° and a neutron flux of approximately 5×10^7 neutrons/cm^2/sec. The irradiated pellets were aged to decay undesirable radionuclides and were then pan-coated with lipid material and encapsulated. The preparation was analyzed chemically for radioactivity. A Ge(Li) detector coupled to a multichannel analyzer was used for the analysis of gamma emitters and a Si(Li) was used with the same analyzer for the x-ray analysis of ^{55}Fe. Each capsule contained 167 mg dried ferrous sulfate USP, equivalent to 50 mg elemental iron, and 0.50 μCi ^{55}Fe. The elixir contained 44 mg of elemental iron/5 ml. Ferrous sulfate was added to yield a dose of 50 mg of elemental iron/5 ml. Immediately before taking the elixir, $^{59}FeSO_4$ (New England Nuclear) was added to give 0.20 μCi ^{59}Fe/5 ml dose.

Administration of test doses. Both iron preparations were taken between 7 and 9 A.M. after an overnight fast. To reduce the effect of day-to-day variability in iron absorption, the following multiple-dose technic[5] was used: On the first morning of each study, half of the subjects were given 5 ml ferrous sulfate elixir while the remaining subjects were given the CR capsule. The two formulations were then given on alternated successive days for a total of 10 days. Each subject received five doses of both preparations. The total dose of radioactivity taken by each subject was 2.5 μCi ^{55}Fe and 1 μCi ^{59}Fe.

Three separate studies were performed. In the first iron was taken by fasting subjects with a small volume of water. No further intake by mouth was allowed for 3 hr. In the remaining two studies, performed in 15 subjects each, the labeled iron was taken with one of two standardized meals.[11] Meal A, considered a typical breakfast, consisted of an Egg McMuffin, bran flakes, and milk; all of these items are believed to strongly inhibit the assimilation of dietary iron. Meal B consisted of a hamburger, french fried potatoes, and a milkshake; because this meal included meat it is generally considered less inhibitory to iron absorption. Most the food items were purchased on the morning of the study from a local McDonald's restaurant.

The chemical compositions of meals A and B (Table I) were obtained from food composition tables[36] or by chemical analyses performed by WARF Institute, Inc. It was assumed that the

small difference in energy and iron content of the two meals would not affect percentage absorption of iron. The ^{59}Fe elixir or ^{55}Fe CR capsule was taken midway through the two meals and no additional food was allowed for 3 hr.

Determination of iron absorption. The subjects returned 14 days after the final test dose was taken. At this time sufficient blood was obtained to permit duplicate measurements of ^{55}Fe and ^{59}Fe radioactivity in 10 ml whole blood. Standards representative of each test dose were processed simultaneously. Radioactivity was measured by liquid scintillation counting on samples prepared by a modification of the method of Eakins and Brown.[16] Sufficient counts were obtained to reduce the error of the net counting rate to less than ±2% in subjects who absorbed more than 1% of the administered test dose. Percentage absorption of both isotopes was calculated on the assumption that 80% of the absorbed dose was incorporated into circulating red cells 14 days after the final test dose. Total blood volume was calculated from the sex, height, and weight of each subject.[6]

In the two studies in which iron was taken with food, retention of whole-body ^{59}Fe was measured immediately before the blood sample was drawn on the final test day. These measurements were obtained with a whole-body counter that consisted of four 6-inch NaI (Tl) crystals and a mobile cot. Total body ^{59}Fe radioactivity was measured during a single 10-min traverse of the patient as described.[12]

Statistical analysis. Because of skewed distribution of iron absorption data, the mean values and standard deviations were calculated on a logarithmic scale. The results were retransformed as logarithms to recover the original units.[9, 23] Statistical comparison of absorption from the elixir and CR capsule was based on a Student's t test to determine whether the mean logarithm of ^{55}Fe:^{59}Fe absorption ratio differed from 0.

Results

Iron absorption data for all three studies are listed in Table II. When the two iron preparations were taken without food, iron absorption means of 4.38% and 4.92% were observed with the CR capsule and elixir. Although absorption ranged widely from 1.05% to 18.45%, the absorption ratio in individual subjects varied from only 0.53 to 1.50 (Fig. 1). The mean CR capsule:elixir ratio of 0.89 (±1 SEM, 0.83 to 0.96) did not reflect a significant difference in absorption ($t = 1.58$, $P > 0.05$).

In contrast with studies in fasting subjects, there were significant differences in absorption when the two preparations were taken with food. For meal A, mean absorption of CR iron decreased from a fasting mean of 4.38% to 3.21%, while absorption fell from 4.92% to 1.02% when taken as elixir. The absorption ratio for CR capsule:elixir was above one in all subjects, with an average ratio of 3.13 (±1 SEM, 2.84 to 3.44); the difference in absorption was significant ($t = 11.85$, $P < 0.0001$).

When the two iron preparations were taken with meal B, mean absorption of 1.69% from the elixir was higher than the 1.02% with meal A, whereas mean absorption from the CR capsule of 2.87% was of the same order as the mean of 3.21% with meal A. With meal B, the mean absorption ratio of CR capsule:elixir was 1.70 (±1 SEM, 1.59 to 1.82), which reflected a significant difference in absorption between the two formulations ($t = 7.76$, $P < 0.0001$).

In the second and third studies, in which absorption was also determined by whole-body counting, there was satisfactory agreement between the whole-body counting values and the results based on measurements of incorporated ^{59}Fe red cell radioactivity. In the combined group of 30 subjects there was a mean absorption value of 1.41% with each of the two technics. Nevertheless, with low absorption whole-body counts were less reliable because the net counting rate frequently was only 5% to 10% above background radioactivity. Duplicate blood determinations in these subjects, however, were highly consistent. Percentage absorption of iron was therefore calculated from measurements of blood radioactivity rather than from whole-body counts.

The wide range in iron absorption between subjects is typical of that reported,[9, 23] but despite this high subject-to-subject variability, there was excellent correlation between ^{59}Fe and ^{55}Fe absorption in the same subject which reflects, in part, the advantage of multiple-dose

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Table II. *Iron absorption from CR iron*

Subject No.	Sex/age	Packed cell volume (%)	Serum ferritin (ng/ml)	Iron absorption: Blood: Spansule (% of dose)	Iron absorption: Blood: Elixir (% of dose)	Iron absorption: Whole-body counter	Absorption ratio (Spansule: elixir)
Fasting							
1	M24	47	71	1.05	1.96		0.53
2	M25	49	142	2.26	3.03		0.75
3	M24	46	138	3.50	3.08		1.14
4	M22	51	152	2.60	3.11		0.84
5	M23	48	109	3.01	3.93		0.77
6	M24	47	80	4.99	4.04		1.23
7	M26	48	52	1.58	4.08		0.39
8	M27	44	29	7.39	4.94		1.50
9	M26	49	18	12.79	13.25		0.97
10	F28	40	113	2.19	2.70		0.81
11	F37	44	82	2.80	3.10		0.91
12	F27	41	59	4.23	3.13		1.35
13	F22	45	101	3.66	3.23		1.12
14	F29	43	103	3.49	4.35		0.80
15	F23	40	35	4.49	4.74		0.95
16	F34	48	106	5.64	6.80		0.83
17	F26	44	33	5.31	8.23		0.65
18	F35	45	59	14.74	10.84		1.36
19	F28	39	44	13.53	15.18		0.89
20	F29	43	14	17.06	18.45		0.92
Mean	27	45	64*	4.38*	4.92*		0.89*
Meal A							
1	M20	43	176	1.55	0.37	1.26	4.18
2	M29	49	170	0.56	0.50		1.12
3	M22	42	103	2.35	0.50	0.89	4.70
4	M27	41	84	1.41	0.51	0.54	2.76
5	M31	52	95	1.73	0.55		3.14

*Geometric mean

administration. For example, the correlation coefficient between absorption of the elixir and CR capsule was 0.95 in fasting subjects and 0.98 and 0.99 with meals A and B. These high correlation values are reflected in the narrow range of absorption ratios in the three experiments (Fig. 1). For example, in the study with fasting subjects, the 95% confidence limit for the mean ratio of 0.89 is 0.77 to 1.03. This indicates that a difference in absorption of more than 15% would have been significant.

There was excellent correlation between iron absorption and body iron stores as measured by serum ferritin, a relationship that has been reported.[10] In all three experiments the absolute correlation coefficient for the relationship between log serum ferritin and iron absorption was greater than 0.80. The relationship between serum ferritin and CR capsule absorption from a meal is shown in Fig. 2.

Discussion

Gastrointestinal side effects occur in 10% to 25% of patients taking iron by mouth. Upper gastrointestinal symptoms such as epigastric pain, nausea, and vomiting are the most common effects, and occur with increased frequency as the dosage is increased. Lower gastrointestinal symptoms such as diarrhea and constipation occur less frequently and are not related to the dose of iron. Side effect studies have demonstrated that 5% to 15% of patients on placebo will develop similar gastrointestinal symptoms,[20, 24, 27] indicating that these

Table II. *Cont'd*

Subject No.	Sex/age	Packed cell volume (%)	Serum ferritin (ng/ml)	Iron absorption: Blood: Spansule (% of dose)	Iron absorption: Blood: Elixir (% of dose)	Iron absorption: Whole-body counter	Absorption ratio (Spansule: elixir)
6	M20	51	28	3.65	1.36		2.68
7	F27	41	85	1.13	0.22	0.65	5.13
8	F20	39	41	1.61	0.33	0.73	4.87
9	F27	41	47	3.40	1.12	1.42	3.03
10	F27	39	15	5.48	1.41	2.20	3.88
11	F24	36	17	5.02	1.87	1.92	2.68
12	F32	41	11	9.10	2.86	2.66	3.18
13	F27	41	22	9.76	2.88	3.77	3.38
14	F27	39	12	9.58	3.67	3.55	2.61
15	F25	42	16	15.25	6.35	5.67	2.40
Mean	26	42	41*	3.21*	1.02*	1.62*	3.13*
Meal B							
1	M32	47	74	0.97	0.50	0.29	1.94
2	M25	44	105	1.07	0.66	1.04	1.62
3	M24	45	114	1.51	0.83	0.91	1.81
4	M31	43	187	1.65	1.82	0.96	0.90
5	F26	44	208	0.43	0.32	0.13	1.34
6	F28	45	103	1.31	0.82	0.61	1.59
7	F23	41	42	1.96	0.86	0.50	2.27
8	F55	42	120	1.88	1.42	0.96	1.32
9	F44	42	45	2.63	1.88	1.98	1.39
10	F25	41	25	7.03	2.75	2.09	2.55
11	F31	41	12	7.27	3.03	2.77	2.39
12	F32	42	22	7.38	3.61	2.81	2.04
13	F23	44	20	6.55	3.78	3.19	1.73
14	F23	40	64	8.38	4.96	2.62	1.68
15	F24	38	25	26.57	15.77	12.62	1.68
Mean	30	43	56*	2.87*	1.69*	1.26*	1.70*

symptoms have a significant psychogenic component.

To avoid the gastrointestinal side effects of iron, a variety of preparations have been marketed in which the solubilization of iron in the gastrointestinal lumen is delayed. It is assumed that gastric irritation is decreased by reducing the peak concentration of ionized iron in the stomach or small intestine. There are three types of CR preparations. With the erosion type the iron salt is mixed with an excipient designed to dissolve more slowly in the gastrointestinal tract. The elution type consists of a physiologically inert plastic matrix containing minute interstices into which the iron is dispersed; this iron is then eluted in the gastrointestinal lumen as secretions gradually diffuse into the central core of the tablet. In the pelleted type iron is contained in numerous pellets that are administered in a gelatin CR capsule. The pellets are coated with blends of selected waxes and fats that dissolve in the gastrointestinal lumen at differing rates. By varying both amount and chemical property of the pellet coating, drug release can be varied from a few minutes to several hours.

A number of studies have demonstrated that gastrointestinal side effects occur less frequently with CR iron than with conventional iron therapy. The most complete study of this type was performed in 1166 blood donors by Rybo and Solvell.[33] Two groups of subjects took ferrous sulfate containing 100 mg elemental iron twice daily, either as a conventional iron

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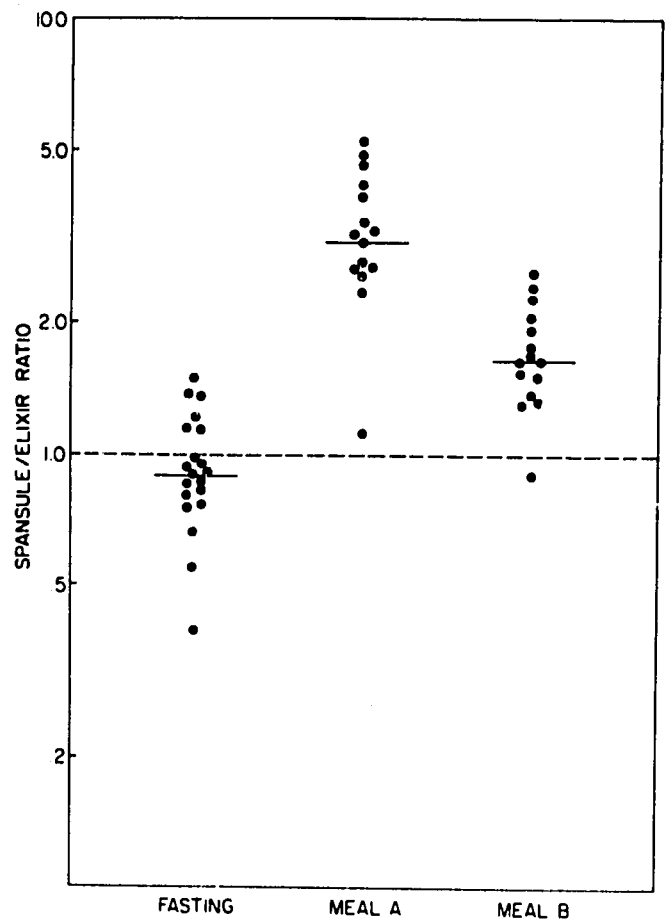

Fig. 1. Absorption of iron from a CR capsule expressed as a ratio with absorption from ferrous sulfate as an elixir. *Horizontal lines* represent geometric means. When taken with food, absorption from the CR capsule is higher.

tablet or as an elution-type CR formulation; a third group took a placebo. Although no difference in the frequency of constipation or diarrhea was observed between the two iron formulations, there was a higher frequency of nausea and epigastric pain with conventional ferrous sulfate than with CR iron and placebo. Such results were also reported in earlier studies.[32, 37]

Because the gastrointestinal absorption of iron is confined to the early segment of the small intestine, it is generally assumed that any delay in the release of administered iron will carry it beyond the site of maximal absorption. Many studies have been performed to determine the absorption of CR iron formulations, but the findings have been quite varied. Some of these disparities can be attributed to a lack of precision in technics for measuring iron absorption. For example, a common approach in earlier studies was to measure the hemoglobin response in patients with iron-deficiency anemia. Studies of CR iron alone have demonstrated therapeutic efficacy[22, 34] and comparative studies have shown that CR iron leads to a therapeutic response equal to or better than conventional iron tablets,[21, 32] but hemoglobin response curves are not a sensitive index of iron absorption. This is particularly so when the dose of oral iron is in excess of that needed to obtain an optimal hematologic response.

Serum iron tolerance curves have also been used to assess the absorption of therapeutic iron and have provided evidence that the absorption of CR iron is equal to[28] or less than[25] con-

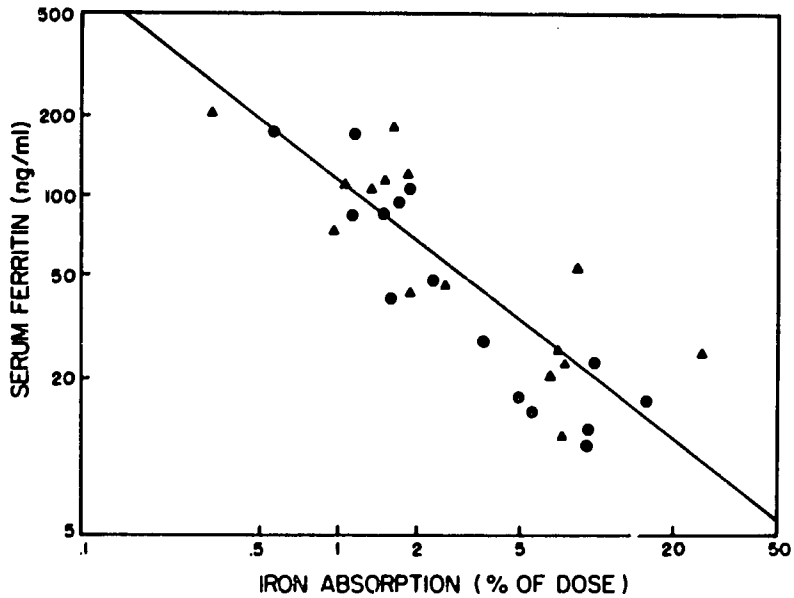

Fig. 2. Correlation of iron absorption from a CR capsule when taken with food and serum ferritin measurements. Measurements after both meal A (●) and meal B (▲) are included.

ventional iron tablets. It should be noted that if the dissolution of iron in the gastrointestinal tract is delayed, serum iron response may not be a suitable index of total absorption. In a recent study, however, it was shown that rapidly disintegrating iron tablets and CR iron induce much the same order of serum iron responses and that the serum iron responses after CR iron correlated with simultaneous isotopic measurements of absorption.[17] The same serum iron response was observed with the two formulations despite the fact that there were major differences in their in vitro dissolution rates.

Much greater precision in studies of iron absorption is afforded by the use of radioisotopic technics. Several studies using isotopes have been performed to measure absorption of CR iron, but their findings conflict. Bothwell et al.[2] reported absorption from a slow-release capsule and from a quick-release preparation. In a later study, absorption of 100 mg CR iron given once daily was compared with the absorption of 33 mg iron as ferrous sulfate given three times a day.[14] Only three of the 12 subjects absorbed more iron from the slow-release than from the conventional iron preparation, but the absorption ratios in this study were highly variable. Subsequent studies with a whole-body counter have not indicated differences in the absorption of conventional iron and CR iron formulations in normal subjects,[7] iron-deficient patients,[1] or patients who had undergone partial gastrectomy.[31]

A number of studies have recently been performed with a multiple-dose double isotope technic to assess absorption from an elution-type CR iron preparation. In an initial report, 100 mg iron as ferrous sulfate was taken twice daily with meals, either as CR or as conventional ferrous sulfate tablets. In normal blood donors, absorption of the CR iron averaged 29% higher than that of the conventional iron tablet; the difference was significant.[30] In later studies performed in blood donors and iron-deficient subjects, the absorption of 100 mg iron in the CR formulation taken twice daily was compared with the absorption of 50 mg iron as ferrous sulfate taken four times a day. Absorption of the two preparations was in the same range in blood donors, but in iron-deficient subjects absorption of CR iron was 25% higher than that after conventional ferrous sulfate forms.[4]

We cannot exclude the possibility that a smaller difference in iron absorption between the two iron preparations would have been ob-

served in patients with overt iron-deficiency anemia. We did include subjects with a wide range in iron status, as reflected by serum ferritin levels. Assuming that 1 ng/ml serum ferritin is equivalent to 10 mg storage iron,[8, 35] iron stores in our subjects ranged from 100 to 2000 mg. The absorption ratio of CR:iron elixir was of the same order at the two extremes in iron stores. For example, with meal A, absorption ratio of CR iron:elixir averaged 3.22 in three subjects with serum ferritins ≤15 ng/ml and 3.33 in subjects with serum ferritins above 100 ng/ml. With meal B, the mean ratio of 2.08 in five subjects with serum ferritins ≤25 ng/ml was higher than the mean ratio of 1.43 in six subjects with serum ferritins above 100 ng/ml ($t = 3.07$, $P < 0.05$). These observations suggest that an even greater difference between absorption of CR iron and elixir may occur in patients with iron-deficiency anemia.

In a recent study the relative absorption of CR and conventional iron was shown to depend not only on iron status, but also on whether the preparations were taken with food.[18] In 16 normal subjects taking 100 mg iron as ferrous sulfate, absorption averaged 7.3% in fasting subjects and was 0.9% when the iron was taken with food. Absorption of CR iron in fasting subjects averaged 5.6%, but was 1.9% when taken with food. These findings are almost identical to ours; we found greater iron absorption when CR iron was given with a meal of either high or low iron availability. In both experiments, absorption of CR iron was lower than that of ferrous sulfate taken in the fasting state.

Because of the higher cost of CR preparations, their use cannot be advocated in all patients who require oral iron therapy. However, studies have consistently demonstrated a lower frequency of gastrointestinal side effects with CR iron than with ferrous sulfate tablets. Our data establish that this can be achieved without reduction in the quantity of iron absorbed. CR preparations provide a safer and less costly alternative to parenteral iron in patients who cannot tolerate oral iron because of gastrointestinal symptoms. Moreover, the less frequent doses required with CR may alleviate, to a certain extent, the poor compliance frequently encountered with oral iron therapy,[27] which is believed to be a major problem with iron supplementation programs in developing countries.

References

1. Baird IM, Walters RL, Sutton DR: Absorption of slow-release iron and effects of ascorbic acid in normal subjects and after partial gastrectomy. Br Med J **4**:505-508, 1974.
2. Bothwell TH, Pirzio-Biroli G, Finch CA. Iron absorption. I. Factors influencing absorption. J Lab Clin Med **51**:24-36, 1958.
3. Boye Nielsen J, Ikkala E, Solvell L, Bjorn-Rasmussen E, Ekenved G: Absorption of iron from sustained release and rapidly disintegrating tablets. Acta Med Scand **194**:123-127, 1973.
4. Boye Nielsen J, Ikkala E, Solvell L, Bjorn-Rasmussen E, Ekenved G: Absorption of iron from slow-release and rapidly-disintegrating tablets—A comparative study in normal subjects, blood donors and subjects with iron deficiency anemia. Scand J Haematol **28**:89-97, 1976.
5. Brise H, Hallberg L: A method for comparative studies on iron absorption in man using two radioiron isotopes. Acta Med Scand **376**(suppl.):7-22, 1962.
6. Brown E, Hopper J, Hodges JL, Bradley B, Wennesland R, Yamaushi M: Red cell, plasma, and blood volume in healthy women measured by radiochromium cell-labeling and hematocrit. J Clin Invest **41**:2182-2190, 1962.
7. Callender ST, Warner GT: Absorption of "Slow Fe" measured with a total body counter. Curr Ther Res **13**:591-594, 1971.
8. Charlton RW, Derman D, Skikne B, et al: Anaemia, iron deficiency and exercise: Extended studies in human subjects. Clin Sci Mol Med **53**:537-541, 1977.
9. Cook JD, Layrisse M, Finch CA: The measurement of iron absorption. Blood **33**:421-429, 1969.
10. Cook JD, Lipschitz DA, Miles LEM, Finch CA: Serum ferritin as a measure of iron stores in normal subjects. Am J Clin Nutr **27**:681-687, 1974.
11. Cook JD, Monsen ER: [illegible] iron absorption. I. Use of a semisynthetic diet to study absorption of nonheme iron. Am J Clin Nutr **28**:1289-1295, 1975.
12. Cook JD, Palmer HE, Pailthorp KG, Finch CA: The measurement of iron absorption by whole-body counting. Phys Med Biol **15**:467-473, 1970.
13. Crosby WH: Prescribing iron? Think safety. Arch Intern Med **138**:766-767, 1978.
14. Crosland-Taylor P, Keeling DH, Cromie BW: A trial of slow-release tablets of ferrous sulphate. Curr Ther Res **7**:244-248, 1965.
15. Dagg JH: Treatment of iron deficiency and iron overload. Br Med J **2**:494-497, 1974.

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16. Eakins JD, Brown DA: An improved method for the simultaneous determination of iron-55 and iron-59 in blood by liquid scintillation counting. Int J Appl Radiat Isot **17**:391-397, 1966.
17. Ekenved G: Absorption from different types of iron tablets-correlation between serum iron increase and total absorption of iron. Scand J Haematol **28**(suppl.):51-63, 1976.
18. Ekenved G, Arvidsson B, Solvell L: Influence of food on the absorption of different types of iron tablets. Scand J Haematol **28**(suppl.):79-88, 1976.
19. Fairbanks VF, Fahey JL, Beutler E: Clinical disorders of iron metabolism. New York, 1971, Grune & Stratton, pp. 297-304.
20. Hallberg L, Ryttinger L, Solvell L: Side-effects of oral iron therapy. Acta Med Scand **459** (suppl.):3-10, 1966.
21. Israels MCG, Cook TA: New preparations for oral iron-therapy. Lancet **2**:654-657, 1965.
22. Layrisse M: The utilization of iron from a controlled-release dose form. Curr Ther Res **5**:232-237, 1963.
23. Layrisse M, Cook JD, Martinez C, et al: Food iron absorption: a comparison of vegetable and animal foods. Blood **33**:430-443, 1969.
24. Levy F, Andersen P, Ekren T: Absorption and side-effects after peroral administration of sustained release iron tablets. Acta Med Scand **204**:303-310, 1978.
25. Middleton EJ, Nagy E, Morrison AB: Studies on the absorption of orally administered iron from sustained-release preparations. N Engl J Med **274**:136-139, 1966.
26. Miles LEM, Lipschitz DA, Bieber CP, Cook JD: Measurement of serum ferritin by a 2-site immunoradiometric assay. Anal Biochem **61**:209-224, 1974.
27. Mitchell ABS: Oral iron tolerance. Postgrad Med J **50**:702-706, 1974.
28. Mouratoff GJ, Batterman RC: Serum iron absorption tests of a sustained-release form of oral iron. J New Drugs **1**:157-159, 1961.
29. Norrby A, Arvidsson B, Solvell L: Total absorption of iron and haemogloon regeneration during 4 weeks of oral iron therapy—a comparative study of 4 different iron doses. Scand J Haematol **20**(suppl.):33-53, 1974.
30. Norrby A, Solvell L: Iron absorption and haemoglobin regeneration studies on a new sustained release iron preparation. Scand J Haematol **8**:231-240, 1971.
31. Parker AC, Simpson JD, Richmond J: Comparison of absorption of "slow iron" and ferrous sulphate tablets BP in patients following partial gastrectomy. Scott Med J **17**:314-315, 1972.
32. Posner LB, Wilson F: An evaluation of sustained-release molybdenized ferrous sulfate in iron-deficiency anemia of pregnancy. J New Drugs **3**:155-160, 1963.
33. Rybo G, Solvell L: Side-effect studies on a new sustained release iron preparation. Scand J Haematol **8**:257-264, 1971.
34. Stevenson TD: Therapeutic assay of a sustained-release form of oral iron. Curr Ther Res **4**:107-110, 1962.
35. Walters GO, Miller FM, Worwood M: Serum ferritin concentration and iron stores in normal subjects. J Clin Pathol **26**:770-772, 1973.
36. Watt BK, Merrill AL: Composition of foods—Raw, processed, prepared, *in* Agricultural Research Handbook No. 8, Washington, D.C., 1963, U. S. Government Printing Office.
37. Webster JJ: Treatment of iron deficiency anemia in patients with iron intolerance: Clinical evaluation of a controlled-release form of ferrous sulfate. Curr Ther Res **4**:130-134, 1962.
38. World Health Organization Technical Report Series No. 405: Nutritional anaemias. Report of a WHO scientific group, 1968.

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