Combating iron deficiency: daily administration of iron is far superior to weekly administration[1–4]

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INTRODUCTION

On the basis of studies in rats, it has been suggested that iron supplements should not be given daily but rather weekly or twice weekly (1). The reason given is that the intestinal mucosal cells are not able to absorb therapeutic doses of iron given daily because of some blockage of the absorption by the iron retained in the mucosal cells. These cells would thus need to be renewed to ensure that iron absorption can begin again. The life span of mucosal cells in rats has been estimated at ≈3 d. Thus, iron supplementation at weekly intervals should be more rational and more cost-effective than daily supplementation because most of the iron given daily would not be absorbed. Moreover, it is thought that iron supplements given weekly would be associated with fewer side effects because the total amount of iron given would be lower. Compliance might also improve because fewer doses of iron might be needed. The hypothesis that weekly iron supplementation is superior to daily administration has been supported by studies comparing the efficacy of the hemoglobin response, which has been found to be similar regardless of whether supplementation was daily, weekly, or twice weekly (2–4).

Three main questions were addressed in this analysis: Is there a mucosal block during oral iron supplementation that would prevent absorption of a therapeutic dose of iron? Is it possible to meet the high iron requirements in pregnancy by weekly administration of iron? How can results of studies suggesting that therapeutic responses to weekly administration of iron are not different from responses to daily administration be explained given that the present analyses showed that there is no mucosal block?

IS THERE A MUCOSAL BLOCK DURING ORAL IRON SUPPLEMENTATION?

In the classic iron absorption study in dogs by Hahn et al in 1943 (5) there was a reduction in iron absorption from a test dose when the dose was preceded, 1.5 h earlier, by a much larger dose of iron. The concept of a "mucosal block" was thus introduced. Later, Granick (6) found that when high iron doses (20–40 mg/kg body wt) were given to guinea pigs, ferritin crystals were seen in smears of the duodenal mucosa and remained in the cells for up to 3–6 d. These observations suggest that ferritin is involved with the regulation of iron absorption.

The mucosal-block concept was modified by Crosby et al (7, 8) on the basis of a series of comprehensive radioautographic studies on the small intestinal mucosa cells of rats, suggesting that the iron content of the cells in the villi of the duodenal mucosa (related to iron status) controls the absorption of iron. A few years later, this hypothesis was questioned seriously on the basis of results from careful studies in humans that analyzed the relation between iron absorption and duodenal mucosa iron concentrations determined by biopsy (9). In this classic study, no relation was found between iron absorption and the iron content of the mucosa.

In 1960, a series of studies were published from our laboratory on factors influencing the absorption rate of iron in humans, which was measured by using 2 radioiron isotopes simultaneously (10). Radiolabeled iron, at therapeutic doses, was infused at a constant rate into the stomach or the duodenum for several hours. The rate of appearance of radioiron in plasma was converted to the rate of absorbed iron by simultaneously measuring the rate of outflow of iron from plasma by using another radioiron isotope that had been administered intravenously. The results of these studies, which lasted several hours, did not indicate a mucosal block in the transfer of iron through the mucosa (11).

In a simple study by Hallberg and Sölvell in 1970 (12), in which 3 oral doses of 75 mg Fe were given daily to a patient with iron deficiency anemia, the first morning dose induced an increase in plasma iron that was similar to the increase seen after the following 2 doses. This observation was not compatible with the prevailing mucosal-block concept. In another study, we tested the effect on hemoglobin regeneration of 4 compared with 3 doses of 74 mg Fe (elemental ferrous iron) daily on alternate days for 10 d given to 5 patients with iron deficiency anemia. Hemoglobin regeneration was considered to occur if the patients were able to maintain a high plasma iron concentration,

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[2] The concept of weekly administration of iron was discussed in a general debate at the 16th International Congress of Nutrition in Montreal, July 28, 1997. This article summarizes some of the main points of this debate that seriously questioned this concept.

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even during the night. There was markedly higher iron absorption in all subjects after 4 doses than after 3 doses. The average increase in absorption was 60%. Although the main purpose of these early studies was not to determine the existence of a mucosal block, the results suggest that there is no mucosal block during oral iron therapy.

Two groups (13, 14), however, did recently examine directly whether there is a mucosal block during oral iron therapy. One group determined iron absorption from a radioiron-labeled dose of 50 mg Fe (ferrous sulfate) given alone (treatment A: total dose: 50 mg) or after the subjects had received 50 mg Fe/d for 6 d (treatment B: total dose of 350 mg) (13). Iron was given between meals (study 1) or with meals (study 2). In study 1, absorption was 9.8% (5 mg) after treatment A and 8.5% (30 mg) after treatment B. In study 2, absorption was 2.6% (1.3 mg) after treatment A and 2.3% (8.0 mg) after treatment B. There were no significant differences in the absorption rate between treatments A and B in either study. Thus, ≈6 times more iron was absorbed when the same dose was given daily than when given weekly.

Another group reported the results of 2 different studies, each of which used 2 different radioiron isotopes (14). In study 1, iron absorption from 60-mg Fe doses given daily for 6 d was compared with the absorption from the same total amount of iron (360 mg) but given as 120-mg doses once a week for 3 wk (study 2). There were no significant differences in the absorption rate of iron (mean: study 1, 8.9%; study 2: 10.9%). The design was similar to the one used by Cook and Reddy (12). Iron absorption from a 60-mg dose was measured in one group of subjects and compared with the absorption from the same dose preceded by 6 daily doses of iron. There was no significant difference in the absorption rate after adjustment for differences in iron status by using the absorption from a 3-mg reference dose in each subject (14).

In the original studies in rats comparing iron absorption from daily therapeutic iron doses with doses given at 3-d intervals, daily iron administration was associated with a continuous decrease in iron absorption (1). This decrease was considered to be due to a mucosal block or was considered a "localized iron overload." Data from my laboratory (15, 16) collected in humans was used to support the interpretation of the findings of Viteri et al (1). In these studies (15, 16), iron absorption was measured in 26 patients with iron deficiency anemia after they consumed therapeutic doses of 100 mg Fe 3 times daily for 10 d and thereafter at 10-d intervals for up to 50 d. Iron absorption was measured with a whole-body counter. In the first 10 d of treatment, the mean increase in absorption was 29.9% (P = 0.0025). Norrby (15) and Norrby and Sölvell (16) interpreted the first 10 d of treatment as being a time in which there was an expansion of the red cell precursors in the marrow associated with a marked increase in the reticulocyte count, which explains the observed initial increase in iron absorption. After 10 d there was a continuous decrease in iron absorption during the 50 d the subjects were examined regularly (**Figure 1**).

This decrease in iron absorption should not be interpreted as a failure of the mucosal cells to absorb and transport iron into the body because the decrease in absorption was found to be directly related to the increase in the concentration of hemoglobin and the decrease in the reticulocyte counts (**Figure 2**). These observations are compatible with the well-known fact that erythropoietic activity is a main determinant of iron absorption after therapeutic doses of iron (17). All of these studies in humans from different laboratories using completely independent methods clearly showed that there is no mucosal block during iron supplementation that is responsible for a reduction in the absorption of iron.

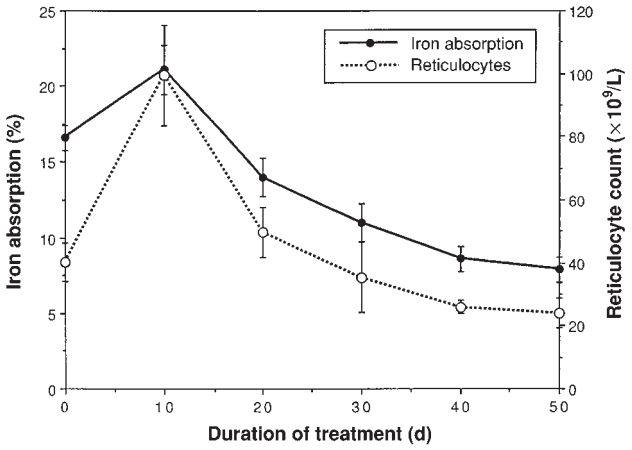

FIGURE 1. Iron absorption during oral iron therapy in relation to changes in the reticulocyte count. The graph is based on data from the study by Norrby and Sölvell (16); 100 mg Fe was given 3 times daily. The absorption from one 100-mg Fe dose was measured at 10-d intervals.

HOW CAN RESULTS IN FIELD IRON SUPPLEMENTATION STUDIES SUGGESTING A SIMILAR HEMOGLOBIN RESPONSE TO WEEKLY AND DAILY IRON ADMINISTRATION BE EXPLAINED ?

It is obvious from the studies reported above that there is no mucosal block in the absorption of iron when given daily. Quantitatively, ≈6 times more iron is absorbed when a specific amount of iron is given daily than when given weekly. The findings in several field studies that the therapeutic response in groups given iron daily was the same as or almost the same as responses when iron was given at weekly or twice weekly intervals may thus seem paradoxical. It is therefore important to try and find some explanation. The experimental design in studies comparing therapeutic efficiency must be carefully chosen to ensure definitive evaluation of whether as much iron is absorbed from weekly as from daily iron administration. Such comparisons should be based mainly on the hemoglobin response because changes in serum ferritin concentrations do not occur until optimal hemoglobin concentrations are reached. Even after this occurs, valid evaluations of serum ferritin changes require that a steady state has been reached.

If relatively high iron doses are given for a long time to subjects with low-grade anemia, then all doses of iron, all dosage schedules, and all iron preparations will give the same hemoglobin response and will thus give the same final, optimal hemoglobin concentration in all treatment groups, incorrectly suggesting that the efficacies of the treatments compared were the same. A different experimental design might have shown, for example, that one preparation or one dosage schedule produced the same result within a much shorter time or with a much lower iron dose.

Several studies have been reported on the effect of weekly administration of iron but only 5 peer-reviewed papers have been published. One of these studies was not available at the time of the debate but is now also commented on (18). In one study of 2–5-y-old preschool children (19), 30 mg Fe was given daily or

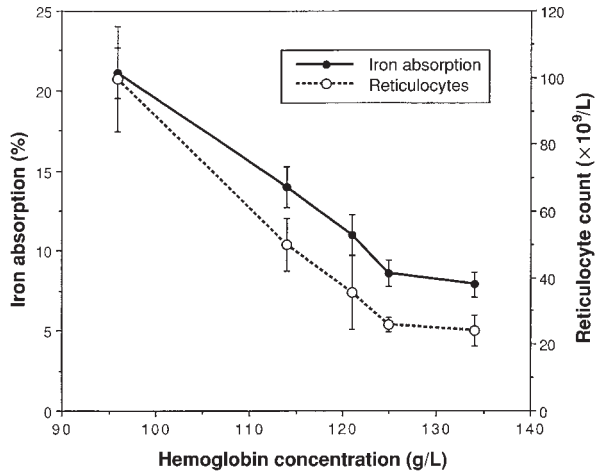

FIGURE 2. Changes in iron absorption and reticulocyte count in relation to the hemoglobin response. The graph is based on data from the study by Norrby and Sölvell (16); 100 mg Fe was given 3 times daily.

twice weekly for 2 mo. No statistically significant difference in hemoglobin response was noted between the 2 groups. The mean initial deficit in hemoglobin was only 5% in the group who received iron daily (baseline: 104 ± 11 g/L; final: 117 ± 8 g/L) and 11% in the group who received iron twice weekly (108 ± 11 g/L; final: 114 ± 10 g/L). No placebo group was included to evaluate a regression toward the mean of the hemoglobin values. Because of this very-low-grade hemoglobin deficit and as a result of the long treatment with high doses of iron in these 12-kg children, only very small amounts of iron were needed to be absorbed for these children to reach their optimal hemoglobin concentrations. This study did not allow conclusions to be made about the relative value of the 2 treatment schedules tested.

Another peer-reviewed paper about preschool children was conducted at high altitude in Bolivia (20). High doses of iron (3–4 mg Fe/kg body wt) were given to children aged 3.3–8.3 y for 16 wk. The initial degree of anemia was low, with a hemoglobin deficit of only 10% in the group given iron once weekly (baseline: 135.3 ± 12.6 g/L; final: 150.5 ± 6.9 g/L) and 10% in the group given iron 5d/wk (baseline: 131.5 ± 12.6 g/L; final: 150.1 ± 6.7 g/L). This study included a placebo group but otherwise it had the same weaknesses as the previous study (19). Thus, no valid conclusion could be drawn about the relative value of the 2 dosage schedules. The final hemoglobin concentration should have been the same after this long period of treatment with these high doses of iron.

One study in preschool children compared the effects of daily administration of iron with that of weekly and twice weekly administration (21). Again, very high doses of iron (75–120 mg elemental Fe) were given to children aged 3–6 y. The results are impossible to evaluate, however, because the treatment periods were not reported.

The most recent study comparing the effect of daily administration of iron (60 mg) compared with that of weekly administration (60 or 120 mg Fe) was made in Indonesian female adolescents (22). A placebo group was included. The anemia was very low grade, <5% in all 3 groups given iron. The hemoglobin response after 8 and 12 wk was similar in these 3 groups. In the group given 60 mg/d, the hemoglobin concentration was 127.6 ± 11.0 g/L at baseline and was 133.9 ± 9.9 g/L after 8 wk. In the group given 60 mg/wk, the hemoglobin concentration was 124.9 ± 10.6 g/L at baseline and was 131.0 ± 8.9 g/L after 8 wk. In the group given 120 mg/wk, the hemoglobin concentration was 126.2 ± 10.6 g/L at baseline and was 131.2 ± 8.8 g/L after 8 wk. The fact that dosages of 60 and 120 mg/wk and 60 mg/d gave similar final hemoglobin concentrations again illustrates that it is not possible to validly compare these regimens after such a long treatment period in subjects with a low-grade hemoglobin deficit given high iron doses.

Only one study in adult women has been reported, in a research letter (23). Two groups were compared: one group (n = 42) was given 60 mg Fe/d and another group (n = 38) was given the same dose weekly for 9 wk. Tablet distribution and compliance were supervised; however, there was no statistically significant difference in hemoglobin response. Because the hemoglobin response was small (a considerable fraction of the women were still anemic after treatment), because other causes of anemia were not addressed, and because a placebo group was not included, it was impossible to make a valid comparison of the efficacy of the 2 treatment models.

It has been hard to understand why the much higher iron absorption observed in well-controlled studies when iron is given daily instead of weekly is not reflected in the results obtained in field studies comparing the 2 regimens. The similar hemoglobin response observed in groups given the 2 treatments can be fully explained, however, by the experimental design used in the field studies. The subjects studied had low-grade anemia and were given high iron doses for a long time before the changes in hemoglobin concentration were compared. This design will conceal the probably much higher absorption from the iron given daily. It should be emphasized that iron therapy in healthy, iron-replete individuals does not cause an increase in the hemoglobin concentration (17).

IS WEEKLY ADMINISTRATION OF IRON IN PREGNANCY A REALISTIC ALTERNATIVE?

Pregnancy is a main indication for iron supplementation and weekly administration of iron has been suggested recently. Pregnant women are a primary main target for iron supplementation, especially in developing countries, because their iron status is of great importance for their own health, the outcome of their pregnancy, and the development of their fetus. It is therefore of interest to examine to what extent weekly doses of iron might meet iron requirements in pregnancy.

A rough calculation suggests that the total iron requirement during pregnancy is ≈800–1000 mg, depending on body size (24, 25). If a woman is moderately anemic (hemoglobin concentration of ≈100 g/L) at the start of pregnancy, the iron requirement would be 400 mg greater, or 1200–1400 mg. Dietary iron absorption is increased during the last half of pregnancy. From some typical diets in developing countries it is possible for 200–300 mg Fe to be absorbed during the 150 d of the latter half of pregnancy. If there are no iron stores, which is common in women in many developing countries, the net iron deficit would amount to ≥600–700 mg.

If 60 mg Fe is given weekly, optimistically, 20% (or 12 mg) would be absorbed weekly. If a higher iron dose is given, eg, 120 mg, the percentage absorption might be somewhat reduced and the absorption might amount to 20 mg/wk. Treatment for 16 wk would result in ≈200 and 300 mg of total iron absorbed from

dosages of 60 and 120 mg, respectively. With a 10-wk period of treatment, which is quite common in developing countries, the corresponding amounts of iron absorbed would be 120 and 200 mg, respectively. The iron deficits would thus be considerable. A daily dose of 60 mg would make up for the iron deficit whereas a weekly dose of 60 mg would only make up 20%, or at most 30%, of the iron deficit.

It is important to emphasize that the period available for supplementation in pregnancy is often short because many women seek prenatal care late in the pregnancy. Also, the efficacy of iron supplementation is important not only for the mother but for her fetus as well because the iron status of the fetus is dependent on the iron status of the mother. The choice of supplementation strategy in pregnancy is thus an important public health measure.

Only one study comparing weekly and daily administration of iron in pregnancy has been published in a peer-reviewed journal (26).This study is therefore important for the evaluation of the ethical correctness of giving iron only once per week instead of daily in pregnancy. Two groups of pregnant women were compared. One group was given 60 mg/d and the other 120 mg/wk; no placebo group was included. Initial hemoglobin values were ≈100 g/L in both groups and supplementation lasted 11.3 wk on average. The final hemoglobin values were 109 and 106 g/L in the 2 groups, respectively. These values are lower than any value reported in the many well-controlled studies in both developing and developed countries (27). In fact, the final hemoglobin values reported in this study were not different from those of corresponding placebo groups in earlier studies (27).The authors seem to be satisfied with the observation that weekly administration was as effective as daily administration. The main finding, however, was that both regimens were equally ineffective. The main finding in the study by Ridwan et al (26) was that weekly administration of iron is economically advantageous and that the distribution of tablets was simpler. It should be emphasized that Ridwan et al's study had no placebo group, the inclusion of which has been strongly recommended by different organizations, and there was no supervision of the intake of tablets. Low compliance was a probable cause of the results. This interpretation is compatible with a recent report from the same country (22). Thus, it is almost impossible to draw any valid conclusions from this study.

CONCLUSION

It is astonishing, to say the least, that multicenter studies of weekly administration of iron were started before there was any clear evidence that a mucosal block existed in humans that reduces the efficacy of daily oral iron therapy, and before any well-controlled and well-designed studies had shown that weekly supplementation of iron was more effective than daily supplementation.

It is also astonishing that the recommendations published by the International Anemia Consultative Group in cooperation with the WHO and UNICEF (28) about the design and interpretation of iron supplementation studies have not been followed. These recommendations include the use of a placebo group, the use of 2 dose levels of iron, the random allocation of subjects to different groups after an initial hemoglobin screening to ensure similar degree of anemia in all groups, and a double-blind design to reduce the classic effect of regression toward the mean (28).

In some of the field studies conducted previously, the prevalence of side effects has been reported even though no placebo group had been included and a double-blind design had not been used. One argument in support of a weekly dosage schedule is that it is more economical than a daily dosage schedule. This is not true, however, because the cost per milligram of absorbed iron is about the same with weekly and daily regimens. I see no scientific basis to change the well-established regimen of daily supplementation of iron-deficient populations to a weekly regimen. This is especially important to emphasize in pregnancy because a weekly regimen can seriously harm both the mother and fetus. There is no evidence supporting an advantage of weekly supplementation over daily supplementation in preventing iron deficiency because the fundamental argument, a mucosal block, is nonexistent. A main challenge of iron supplementation programs is to find more effective ways to improve compliance. Systematic efforts are urgently needed and are a major challenge to UNICEF and the WHO.

REFERENCES

1. Viteri FE, Xunian L, Tolomei K, Mai A. True absorption and retention of supplemental iron is more efficient when iron is administered every three days rather than daily to iron-normal and iron-deficient rats. J Nutr 1995;125:82–91.
2. Galloway R, McGuire J. Daily versus weekly: how many iron pills do pregnant women need? Nutr Rev 1996;54:318–23.
3. Yip R. Iron supplementation during pregnancy: is it effective? Am J Clin Nutr 1996;63:853–6.
4. Solomons NW. Daily versus weekly iron: we still might not be asking the right questions. Nutr Rev 1997;55:141–2.
5. Hahn PF, Bale WF, Ross JF, Balfour WM, Whipple GH. Radioactive iron absorption by the gastro-intestinal tract. Influence of anemia, anoxia, and antecedent feeding. Distribution in growing dogs. J Exp Med 1943;78:169–88.
6. Granick S. Ferritin. IX. Increase in the protein apoferritin in the intestinal mucosa as a direct response to iron feeding. The function of ferritin in the regulation of iron absorption. J Biol Chem 1946;164:737–46.
7. Conrad ME, Crosby WH. Intestinal mucosal mechanisms controlling iron absorption. Blood 1963;22:406–15.
8. Crosby WH. Editorial review: the control of iron balance by the intestinal mucosa. Blood 1963;22:441–9.
9. Allgood JW, Brown EB. The relationship between duodenal mucosal iron concentration and iron absorption in human subjects. Scand J Haematol 1967;4:217–29.
10. Hallberg L, Sölvell L. Determination of the absorption rate of iron in man. Acta Med Scand 1960;168(suppl 358):3–17.
11. Hallberg L, Sölvell L. Iron absorption studies. Acta Med Scand 1960;168(suppl 358):3–108.
12. Hallberg L. Oral iron therapy—factors affecting the absorption. In: Hallberg L, Harwerth HG, Vanotti A, eds. Iron deficiency. New York: Academic Press, 1970:551–61.
13. Cook JD, Reddy MB. Efficacy of weekly compared with daily iron supplementation. Am J Clin Nutr 1996;62:117–20.
14. Pizzaro F, Olivares M, Arredondo M, Hertrampf E, Walter T. Does daily iron administration produce a mucosal blockade? Wageningen, Holland: European Academy of Nutritional Sciences, 1997.
15. Norrby A. Iron absorption studies in iron deficiency. Scand J Haematol 1974;suppl 20:1–125.
16. Norrby A, Sölvell L. Iron absorption and haemoglobin regeneration in posthaemorrhagic anaemia—studies on the absorption pattern during oral iron therapy. Scand J Haematol 1974;suppl 20:75–105.
17. Bothwell TH, Charlton RW, Cook JD, Finch CA. Iron metabolism in man. London: Blackwell Scientific Publications, 1979.
18. Angeles-Agdeppa I, Schultink W, Sastroamidjojo S, Gross R, Karyadi D. Weekly micronutrient supplementation to build iron

stores in female Indonesian adolescents. Am J Clin Nutr 1997;66:177–83.
19. Schultink W, Gross R, Gliwitzki M, Karyadi D, Matulessi P. Effect of daily vs weekly iron supplementation in Indonesian preschool children with low iron status. Am J Clin Nutr 1995;61:111–5.
20. Berger J, Aguayo VM, Téllez W, Luján C, Traissac P, San Miguel JL. Weekly iron supplementation is as effective as 5 day per week iron supplementation in Bolivian school children living at high altitude. Eur J Clin Nutr 1997;51:381–6.
21. Liu X-N, Kang J, Zhao L, Viteri F. Intermittent iron supplementation in Chinese preschool children is efficient and safe. Food Nutr Bull 1995;16:139–46.
22. Schultink W, van der Ree M, Matulessi P, Gross R. Low compliance with an iron supplementation program: a study among pregnant women in Jakarta, Indonesia. Am J Clin Nutr 1993;57:135–9.
23. Gross R, Schultink W, Juliawati H. Treatment of anaemia with weekly iron supplementation. Lancet 1994;344:821 (letter).
24. Hallberg L. Iron balance in pregnancy. In: Berger H, ed. Vitamins and minerals in pregnancy and lactation. Nestlé Nutrition Workshop Series. Vol 16. New York: Raven Press, 1988:115–27.
25. Hallberg L. Iron balance in pregnancy and lactation. In: Fomon SJ, Zlotkin S, eds. Nutritional anemias. Nestlé Nutrition Workshop Series. Vol 30. New York: Raven Press, Ltd, 1992:13–25.
26. Ridwan E, Schultink W, Dillon D, Gross R. Effects of weekly iron supplementation on pregnant Indonesian women are similar to those of daily supplementation. Am J Clin Nutr 1996;63:884–90.
27. Sloan N, Jordan E, Winikoff B. Does iron supplementation make a difference? Arlington, VA: John Snow, Inc, 1992.
28. Baker S, Ramachandran K. The design and analysis of iron supplementation trials. A report of The International Nutritional Anemia Consultative Group (INACG), 1984. Washington, DC: Nutrition Foundation, 1992.