Letters to the Editor

Weekly compared with daily iron supplementation

Dear Sir:

In their paper, Cook and Reddy (1) make an unwarranted and potentially damaging extrapolation from their data. They conclude that “there is no significant absorptive advantage in giving iron less often than once daily” and question whether weekly iron supplementation can “meet the requirements of iron-deficient individuals” and pregnant women. They base these reservations on the absorption of a 50-mg dose of iron ingested with or without food by neither iron-deficient nor anemic women receiving either no iron or 50 mg/d for the previous 6 d. Overall absorption was low, as one would expect, being 13% lower with previous daily iron administration. A fair conclusion is that under these conditions, absorption was slightly lower when the dose was administered daily.

Cook and Reddy’s (1) conclusions are not applicable to the vast iron-deficient populations in developing countries. They did not study for adequate periods of time iron-deficient subjects, pregnant women, or higher iron doses (as WHO recommends during pregnancy), and yet they extrapolate the very low absorption when iron was consumed with food to predict that adequate weekly iron doses cannot supplement food iron to meet the needs of these groups. They did not consider that higher absorption of iron supplements occurs in these populations, particularly when they are consumed without food, and that a greater reduction in absorption could occur with the higher daily doses commonly administered during iron repletion.

Based on the authors’ data (1), 50 mg Fe consumed weekly without food would provide the equivalent of 0.62 mg Fe/d to fertile-age women having some iron reserves and up to 1.5 mg (50 mg × 21.6% absorption/7 d) to those without reserves. These amounts of absorbed iron would supplement food iron to compensate for menstrual losses, decreasing the prevalence of ferropenia to that of the adult male (essentially nil). Fertile-age women would then likely enter pregnancy with adequate iron reserves (preventive supplementation).

It is also not justified, on the basis of the data presented (1), to cast doubt on the efficacy of weekly doses given over several months to prevent and control iron deficiency in at-risk populations (2, 3). The efficacy of weekly doses is being tested in field studies coordinated by the International Iron Nutrition Program of the United Nations University, and results are beginning to appear. A hasty and uncritical acceptance of Cook and Reddy’s results and discussion may generate unwarranted confusion. Published and as yet unpublished results from field trials indicate that weekly iron supplementation is efficacious.

Anemic Indonesian women responded equally well to weekly or daily iron administration (4) as did anemic, ferropenic fertile-age women in Berkeley, CA who received 60 mg Fe/d or weekly, in contrast with control subjects. Serum ferritin concentrations also increased, particularly in nondeficient subjects (5). Equally clear effects have been reported among pubertal girls supplemented weekly in Malaysia (6).

Weekly administration of 120 mg Fe for 4 mo to pregnant Chinese women had the same effect as 60 or 120 mg/d in reducing anemia at term from 52% to 16–17% (7). Similar reductions are being observed in pregnant Guatemalan women receiving 120, and especially 180 mg Fe/wk (F Chew, B Torün, H Mendez, and FE Viteri, unpublished observations, 1995). In preschool-age Chinese children, daily or weekly administration of 6 mg Fe/kg for 3 mo was equally effective in correcting ferropenic anemia, preventing new cases of iron deficiency and bringing iron reserves to normal values or higher (8). None of these results would be possible according to the extrapolations that Cook and Reddy made (1). Also, contrary to their predictions, side effects and rejections of supplementation were significantly lower with weekly supplementation in all the trials where these were evaluated.

Cook and Reddy’s (1) and our (9) recommendation of caution in extrapolating rat data to humans is clear. However, one cannot dismiss the results from our supplementation studies in rats on the basis of the iron doses used. Precisely because of the between-species metabolic differences, extrapolations on the basis of body weight are invalid: normal rats ingest 20 mg Fe · kg⁻¹ · d⁻¹ (10). That would be the equivalent of 1.2 g/d by a 60-kg person. Thus, comparisons are better made in terms of their relation to “normal” intakes. WHO collaborative studies in pregnant women in Burma and Thailand have used daily doses of 120–240 mg Fe (11). These are between 10 and 20 times greater than their usual intake. The supplementation doses used in our rat studies, which clearly showed a greater absorption efficiency by intermittent dosing during iron repletion, were chosen to be 10 times their usual iron intake (9). The statement that these doses “correspond to a potentially lethal dose of several grams of iron when extrapolated to humans on a body weight basis” is, thus, invalid.

Interestingly, absorption of supplementary iron in non-iron-deficient rats (9) was almost identical to that reported in non-iron-deficient subjects (1): 8% mean weighted percent absorption in rats supplemented daily and 9.6% in rats supplemented every 3 d (considered similar to weekly dosing in humans because of the faster intestinal mucosal turnover in rats). Daily supplemented rats absorbed 17% less. In the same studies we observed a significantly greater efficiency in supplemental iron absorption among iron-deficient rats during the process of iron repletion when they were supplemented intermittently rather
than daily. The magnitude of the difference during iron repletion measured at periods when cumulative iron absorption was the same in both groups (rats supplemened daily and rats supplemented every 3 d) showed that the former group absorbed only 53% of the iron that the latter group did.

Initial reports are already sufficient to support the efficacy of a weekly dose under field conditions in developing countries. In light of the arguments presented in this letter, it would be most unfortunate if Cook and Reddy’s (1) paper has the effect of prejudging the final outcome of the current multicenter studies or of inhibiting acceptance of their pragmatic conclusions.

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REFERENCES

Reply to FE Viteri

Dear Sir:

In his haste to defend the intensive marketing of intermittent iron supplementation by international organizations such as the United Nations University, Viteri apparently has not taken the time to read our article adequately. We concluded that "there is no significant absorptive advantage in giving iron less often than once daily." He expresses no concerns about the validity of our findings, only the implications. We believe that the only "fair conclusion" from our data is that in young women who are most susceptible to iron deficiency, there is no scientific evidence that the absorption of an iron supplement is significantly reduced by taking prior daily iron supplements. This finding disagrees sharply with the conceptual basis on which studies of intermittent supplementation have been heavily promoted.

Viteri presents a variety of arguments for why our findings do not apply to "vast iron-deficient populations in developing countries." One of his major concerns is that our subjects were not iron-deficient. However, as stated in our report, >20% of the volunteer subjects had a serum ferritin concentration ≤ 12 μg/L, which is considered to represent iron deficiency by most hematologists. In raising this issue, Viteri implies that the efficacy of intermittent supplementation will be greater in individuals who are more iron-deficient. Our data argue otherwise. We observed a slight tendency to an inhibitory effect of prior iron only in iron-replete subjects. On the other hand, iron absorption in iron-deficient women (serum ferritin ≤ 12 μg/L) averaged 16% with daily iron supplementation as compared with 12.5% with weekly supplementation. This finding is exactly what we would expect from our knowledge of iron transport by the intestinal mucosal cells. In iron deficiency, virtually all of the iron taken into the mucosal cells from the gastrointestinal tract is transported rapidly into the body, leaving little in the cells to inhibit the subsequent uptake of iron from the lumen (1). Perhaps this also explains why daily supplementation does not suppress iron absorption in humans but does in rats, which are a far better animal model for studying iron excess than iron deficiency.

Our study was undertaken to examine the scientific basis for the concept according to which intermittent supplementation has been widely advocated. It is difficult to understand why our findings "may generate unwarranted confusion." What does create confusion is anecdotal reports, letters to scientific journals, and meeting abstracts that do not contain sufficient detail to permit a scientific evaluation of the results. Most of the references cited by Viteri in support of intermittent supplementation fall into this category. It is hard to imagine that reporting the results of field trials in full-length peer-reviewed articles published in widely read scientific journals will "inhibit" their acceptance. Delaying publication in this format should.

One such peer-reviewed report was published recently in which the authors concluded in favor of intermittent supplementation. Schultink et al (2) compared the effect of daily compared with weekly iron supplementation in Indonesian children with low iron stores (2). Eighty-seven children 2-5 y of age with baseline hemoglobin concentrations < 112 g/L were given anthelminthic treatment before randomly assigning them to receive 30 mg Fe as liquid ferrous sulfate either daily or twice weekly for 2 mo. A twofold greater increase in hemoglobin concentration and decrease in erythrocyte protoporphyrin concentration was observed in children given daily compared with weekly supplements of iron, but the difference was not significant after certain statistical adjustments. The true efficacy of either administration schedule cannot be assessed in this study because no control group was included to measure the effect of prior deworming and of regression to the mean of the laboratory measurements. An even more important concern is that despite supervised administration of