

## Weekly Versus Daily Oral Iron Administration: Are We Asking the Right Questions?

*The separation of oral iron doses to conform to the cycle of intestinal mucosa turnover has been suggested by some as a method to improve the efficiency of uptake for therapeutic doses of iron. A short-term study in healthy American women failed to confirm a superior absorption of radioiron with a 7-day interval versus everyday administration of a 50-mg iron dose, but the iron status of the experimental subjects may have produced an inappropriate population on which to test a question relevant to Third World populations.*

In terms of efficacy and efficiency, what is the best dosage schedule for administering oral iron for therapeutic or preventive ends? Recent studies in laboratory rodents<sup>1,2</sup> have reported that giving an oral iron dose every 3 days provides a greater fractional uptake per dose than giving the same amount on a daily basis. As such, it has become an issue that has been called into question from a human perspective, including the proposition by UNICEF to perform key experiments to refine iron-dosing schedules for public health.<sup>3</sup>

In theory, an exemplary contribution of the industrialized world's technology and resources for the benefit of health problems found in developing countries is noted in a recent publication in which women volunteers from Kansas, USA participated in an effort to refine our understanding of the interaction of the dosage schedule for oral iron and its efficiency of absorption.<sup>4</sup> A total of 23 subjects participated on two occasions each, separated by a week of time. Using time-honored radioisotopic methods involving the extrinsic labeling of an oral iron dose with the respective radioisotopes of iron (<sup>55</sup>Fe and <sup>59</sup>Fe),<sup>5</sup> a 50-mg dose of elemental iron as ferrous sulfate was given in several formats. Twelve subjects participated in the segment of the study designed to simulate iron taken on an empty stomach. Half of the subjects initially received 50-mg iron capsules (ferrous sulfate) once daily for 7 days taken between breakfast and lunch, and the other half (presumably) received a single iron capsule on the first day of the study. On day 7, they returned for an oral dose of <sup>55</sup>Fe in aqueous solution. Over the next 6 days, they reversed their oral iron treatments and returned for an aqueous dose of <sup>59</sup>Fe on

day 14. In 11 additional subjects, the same sequence of either 7-day or 1-day separation of iron capsules was applied, with a random order for the two schedules. In addition, the 50-mg radiolabeled doses of iron used for the absorption tests were given with a meal of rice, beans, peas, cabbage, and cauliflower cooked in oil to simulate a meal typical of developing countries.

Generally, there is the expected inverse relationship between iron status as reflected by serum ferritin concentration, and the fractional absorption of the radioiron tracer. Because of such intersubject variance in absolute iron uptake, the findings were expressed as a ratio of the percent iron absorption from the test dose with the daily dosing of 50 mg of iron to that from the test dose after the 7-day interval. A ratio close to 1.0 would suggest equivalency of the two schedules, whereas a ratio of <0.5 would suggest that the weekly dosing permitted twice the absorption of the daily schedule. In the 12 subjects who received aqueous dosing, the geometric mean of the absorption ratio was 0.87; it was also 0.87 in the 11 subjects given their isotopic tracer with a meal. In the meal-format, however, the first subject had a major inversion in the daily/weekly ratio. She had a 13.4% efficiency of iron absorption after daily iron and a 2.41% uptake with the weekly schedule; this calculates to a daily/weekly ratio of 5.6. Given that her ferritin concentration was 8 µg/L, which is an expression of iron deficiency, an iron uptake below 10% is likely an aberration. If we accept that this subject represents a biologic outlier and the data are analyzed with the remaining 10 subjects included, the geometric mean daily/weekly iron absorption ratio becomes 0.70. Even with the nonideal human model (below), this is suggestive of a slight advantage with the weekly iron schedule.

Within the risk groups for iron deficiency, a group of women in the heart of their menstrual years should serve as a reasonably "iron hungry" population for studies of iron-absorbing capacity. However, among the 23 women (aged 21–29 years) enrolled in the study, none were anemic, and only 5 (22%) had a circulating serum ferritin of <12 µg/L, consistent with absent iron stores. The median ferritin value for this population was 19 µg/L, which corresponds to 190 mg of iron reserves as the median status for the subjects as a group. With the selection of such a relatively iron-replete population of subjects, however, the researchers are caught in a classical "floor-ceiling" problem in the design. As iron is a homeostatically regulated nu-

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trient, the bodies of the majority of the Kansas volunteers were as interested in excluding an excess uptake as in building additional iron reserves and hence did not have a great propensity to show high rates of absorption for either of the test doses.

Finally, the theory behind the spacing of dosing is based on the cycle of renewal time for the intestinal mucosa. If dosing is synchronized with this turnover, the iron-blocking response induced by a prior administration of high-dose iron will have been dissipated.<sup>6</sup> Cook and Reddy<sup>4</sup> followed their subjects through only one cycle of either every-day or once-weekly iron. A careful examination of the rodent data of Viteri et al.<sup>2</sup> would suggest that at least two to three cycles are required for the separation of absorption efficiencies to become manifest. Perhaps a 14- or 21-day lead up to the radioisotopic studies in Kansas would have better tested the fundamentals of the underlying theory. Therefore, the paper from Kansas City<sup>4</sup> serves to advance the debate—but perhaps not the *evidence*—needed to develop programmatic policy in Katmandu or Kinshasa.

However, the claims of “superior” absorption efficiency for proponents of the alternate day schedule<sup>6</sup> must be put into context. The net uptake of iron into the body is a function of the fractional absorption efficiency times the amount of iron consumed. It would truly take a “King Midas touch” to expect 50 mg of iron to perform the job of 350 mg! Hence, are we asking the right questions in this debate? It would be an achievement just to have the hematologic response and iron repletion equivalent—or even close to equivalent—between weekly and daily administration. In fact, when populations with typical Third World anemia conditions are compared in the daily vs. the weekly format using the hemoglobin response (a cruder, but more realistic indicator of iron uptake) as the measure, equivalency of daily versus weekly dosing has indeed been reported.<sup>7-9</sup>

From the ultimate programmatic perspective, moreover, two other questions remain. *Is weekly administration of oral iron less traumatic to the organs for its uptake and initial storage?* Intracellular iron is a mediator of oxidation.<sup>10</sup> Viteri<sup>6</sup> has suggested, again from rodent observations, that therapeutic-level dosages of iron represent an oxidative shock. The cumulative deleterious tissue effect would be mitigated by administration in rough synchrony with the human mucosal turnover. *Is compliance improved and distribution simplified with cycled—rather than daily—dosing?* This may be one situation when the proof is not determined by having well-nourished women consume oral iron doses laced with isotopic tracers, but rather in the offering of actual supplemental doses to iron-deficient and anemic women as they live in their poor communities of the developing world. Poor com-

pliance with prescribed iron is a documented limitation to improving iron status.<sup>11-13</sup> If women take as much iron, or even more iron, because the schedule of once weekly is more appealing and the distribution system can be removed from the health-center to a nonmedical, community-based locus, the true bottom line for alternative dosing schedules for iron will appear on the balance sheet. If ongoing research confirms positive answers to the aforementioned questions, it will have addressed the right questions for the pressing problem of dysfunction, debility, and mortality from iron deficiency and anemia among populations with hyperendemic ferroplenia in Africa, Asia, and Latin America.

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