inside blood commentary

22 OCTOBER 2015 | VOLUME 126, NUMBER 17

CLINICAL TRIALS AND OBSERVATIONS

Comment on Moretti et al, page 1981

So you know how to treat iron deficiency anemia

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In this issue of *Blood*, Moretti et al[1] provide data that challenge the entrenched oral treatment of iron deficiency anemia. The paper shows how the newer understanding of hepcidin and iron metabolism in general can lead to very practical improvements in the management of iron deficiency anemia, a disorder that may affect as many as 1 billion people.

The treatment of iron deficiency anemia is settled and established in textbooks, so why does it fail more often than we would like?[2,3] Oral treatment starts with tablets of ferrous sulfate or a similar compound, each containing ~70 mg of elemental iron, preferably taken on an empty stomach 3 times a day. The benchmark for successful treatment is a 2-g/dL hemoglobin increase in 3 weeks.[2,3] A 2-g/dL increase in hemoglobin over 21 days is about 0.1 g/dL hemoglobin per day; if we assume a reasonable blood volume of 5 L, that equates to 0.1 g/dL × 50 dL = a 5-g increase in total hemoglobin per day. The amount of iron in 1 g of hemoglobin is 3.34 mg. Therefore, to make an extra 5 g/dL per day of hemoglobin, we have to take in an extra 17 mg of iron per day. If we assume that only 80% of ingested iron goes to make hemoglobin and that there is a continuing loss of 1 mg of iron per day, we are still only absorbing about 25 mg of iron per day of 200 mg of the elemental ferrous sulfate ingested (~12.5%). Therefore, it is time to wonder whether taking a 70-mg tablet of elemental iron, 3 times a day, every day is the best way to treat iron deficiency anemia. Likely the extra 180 mg of unabsorbed iron contributes to the unpleasant gastrointestinal side effects that some patients report.

That is the key question raised by Moretti et al. Their hypothesis and approach are based on the centrality of hepcidin in iron metabolism. It was only about 15 years ago that we learned about hepcidin and how it controls iron absorption from gut mucosa and iron release from macrophages by interacting with ferroportin, causing its internalization and destruction.[4] Simplistically, the synthesis of hepcidin is controlled by 3 kinds of signals: inflammation prominently represented by interleukin-6, which increases hepcidin synthesis and thus decreases iron absorption; the need for increased erythropoiesis, which sends a signal to decrease hepcidin and allow the absorption of more iron and thus the synthesis of more needed red blood cells; and an iron status signal based on plasma iron levels and iron stores.[4] The last of these is critical for this paper, because if plasma iron or iron stores are increased, the resulting signal increases hepcidin, thereby blocking iron absorption and preventing iron overload.

The authors then raise the question, obvious now, but not previously appreciated, as to whether our current oral treatment of iron deficiency anemia results in a paradoxical interference in iron absorption. Their argument is that absorption of a large oral dose of iron will cause an increase in plasma iron, which in turn will cause an increase in hepcidin, which in turn will interfere with iron absorption of the next dose of iron.

Using elegant technology based on their skills with 3 isotopes of iron, so that subjects could be their own controls, they measured total and fractional iron absorption in several scenarios testing varying doses of oral iron administered over a variety of schedules. Per prediction, they found that ingesting a substantial single dose of oral iron, when absorbed, led to an increase in plasma iron, which in turn led to an increase in hepcidin. The measured increase in hepcidin then impaired iron absorption from subsequent doses of oral iron. This hepcidin effect, suppressing iron absorption, could last as long as 48 hours.

It may be that our orthodox treatment of iron deficiency anemia is all wrong. It results in an ~12% to 15% absorption of iron and produces unpleasant side effects. Rather than administering 1 large iron pill 3 times per day, maybe we should treat iron deficiency anemia by giving a single substantial dose of elemental ferrous iron before breakfast on Monday, Wednesday, and Friday. Recall that we need to absorb only ~180 mg of iron per week to meet and beat the best current program.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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DOI 10.1182/blood-2015-09-666511