Dosing Patients With Oral Iron Supplements:

Practical Guidance

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Abstract

Iron is an essential trace element that is important for the development, structure, and functioning of the brain. Iron has been both favorably and unfavorably implicated in neuropsychiatric disorders. For example, iron adequacy in pregnancy and early childhood has been suggested to reduce the risk of neurodevelopmental disorders and schizophrenia, but iron mechanisms have been implicated in neurodegenerative disorders, multiple sclerosis, and stroke. Supplemental iron may be indicated to treat restless legs syndrome, akathisia, and pica, but more commonly to treat iron deficiency associated with poor nutrition in major mental illness. Supplemental iron is commonly orally administered but is poorly absorbed by this route. It is therefore necessary to know what improves and what impairs iron absorption. This article explains that, for best absorption, oral iron supplements are ideally dosed as ferrous salts. The dose should be administered in the morning, on a fasting stomach, along with about 100 mg of vitamin C in the form of a tablet, or with a glass of orange or other citrus juice. If neither vitamin C nor citrus juice is available, as a poorer option, iron should be dosed with plain water. Absorption is markedly reduced if iron is administered in the afternoon, or with food such as cereals and other grains, or with beverages such as milk, tea, and coffee. Calcium supplements, antacids, H2 inhibitors, and proton pump inhibitors also reduce the absorption of orally administered iron. Some data suggest that alternate day dosing improves fractional iron absorption as well as reduces adverse effects of treatment. Finally, to reduce the risk of pill esophagitis, iron should be dosed with a full glass of liquid, and the patient should not recline or lie down for at least the next 30–60 min.

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Iron is an essential trace element[1] that plays important roles in the brain. It is involved in fundamental physiological processes, ranging from oxygen transport to energy metabolism.[2] It plays a role in critical cellular processes, such as neural cell differentiation,[2] myelination by oligodendrocytes,[3] neurotransmitter synthesis and breakdown,[2] and programmed nerve cell death through ferroptosis.[4] In brief, it is implicated in both cell structure and cell functioning in the brain. This article briefly examines the relevance of iron in neuropsychiatry and focuses on a very practical matter: how to dose oral iron supplements so as to maximize its absorption.

Iron in Neuropsychiatry

Iron adequacy in neonates, infants, and children supports normal brain development and functioning,[5,6] and iron deficiency has been suggested as a risk factor for intellectual disability and developmental delays[7] as well as autism spectrum disorder and attention-deficit/hyperactivity disorders.[6,8] Maternal iron deficiency during pregnancy may be a risk factor for schizophrenia.[9,10]

On the flip side, iron has been implicated in the pathogenesis of neurodegenerative disorders,[11] as in Alzheimer's disease ,[12] Parkinson's disease,[4] Huntington's disease,[13] amyotrophic lateral sclerosis,[14] and Friedreich's ataxia.[15] Iron has been implicated in the pathogenesis of other neurological disorders, as well, ranging from multiple sclerosis[16] to stroke.[17]

Iron may be therapeutic in many neuropsychiatric conditions, such as pica,[18] pagophagia,[19] antipsychotic-induced akathisia,[20] and restless legs syndrome (RLS),[21] including RLS during pregnancy[22] and pediatric RLS.[23] Ferroptosis may be leveraged in glioma therapy.[24,25]

Iron deficiency is often part of the nutritional deficiency that may be observed in patients with psychiatric disorders, such as schizophrenia and depression.[26–28] Correcting iron deficiency requires clinicians to know how to dose supplemental iron. Specific issues, listed in Box 1, were addressed in a recent clinical trial.

Box 1.

Questions Regarding the Administration of Oral Iron Supplements

At what time of day is supplemental iron best administered?
Should supplemental iron be administered on a fasting stomach or after a meal?
Should supplemental iron be administered with water or with a beverage?

The Absorption of Supplemental Iron: Clinical Trial

Much literature has been published on factors that influence the absorption of iron from food, but questions remain regarding the absorption of oral iron supplements. In this context, von Siebenthal et al[29] described an open-label randomized controlled crossover trial of the effects of food, beverages, and time of day on the absorption of supplemental iron.

The study was conducted in Zurich, Switzerland. The sample comprised 34 women aged 18–45 years, all of whom were iron deficient (plasma ferritin <30 µg/L) but none of whom were anemic (hemoglobin >12 g/dL). The median age of the women was 28 years. The mean body weight was 57 kg, and the mean body mass index (BMI) was 20 kg/m^2. All women were nonsmokers and were generally healthy.

On each of different days and in random order, and with (mostly) 1-day intervals between dosing conditions, these women received 100 mg of radiolabeled ferrous fumarate as follows:

1. In the morning, with water (reference condition)
2. In the morning, with 80 mg of ascorbic acid (vitamin C)
3. In the morning, with 500 mg of ascorbic acid
4. In the morning, with coffee
5. In the morning, with breakfast that included coffee and orange juice
6. In the afternoon, with water

In these 6 treatment conditions, morning dosing was at 7:00–9:00 am after an overnight fast, and afternoon dosing, at 4:00–6:00 pm after a 4 hour fast. Breakfast comprised a bread roll, butter, honey, yogurt, orange juice (containing about 90 mg of ascorbic acid), and coffee. After dosing, food and beverages were not permitted for 3 h.

Important findings from the study are presented in Table 1. *In summary*, the median fractional iron absorption was 21% when iron was dosed in the morning with water (reference condition); 27% with ascorbic acid, 80 mg; 31% with ascorbic acid, 500 mg; 10% with coffee; and 7% with breakfast. Fractional iron absorption was 13% when dosed with water in the afternoon. Notably, administration of iron, along with ascorbic acid, in a fasting condition and in the morning, was associated with a 4-fold greater absorption relative to administration of iron with breakfast (despite the breakfast containing ascorbic acid in orange juice).

Table 1.

Fractional Iron Absorption of Ferrous Fumarate (100 mg) in Different Oral Dosing Conditions[a]

Important findings were:
1. The median FIA was 20.6% (IQR, 12.3% to 25.5%) when ferrous fumarate was dosed with water (reference condition).
2. The median FIA was 26.7% (IQR, 19.1% to 32.6%) when ferrous fumarate was dosed with 80 mg of ascorbic acid and 30.5% (IQR, 24.9% to 49.5%) with 500 mg of ascorbic acid.
3. The median FIA was 9.5% (IQR, 6.2% to 16.3%) when ferrous fumarate was dosed with coffee and 6.9% (IQR, 4.1% to 13.0%) with breakfast.
4. The median serum hepcidin level was more than twice as high in the afternoon as in the morning. The median FIA was 12.9% (IQR, 9.9% to 21.6%) when ferrous fumarate was dosed with water in the afternoon.
5. Relative to the reference condition, both doses of ascorbic acid significantly increased FIA. The difference in FIA was not statistically significant between the two doses of ascorbic acid.
6. Relative to the reference condition, FIA was significantly lowered by both coffee and breakfast, and FIA was significantly lower with breakfast than with coffee.
7. Relative to the reference condition, FIA was near-significantly lower in the afternoon than in the morning.

[a]Findings from the study by von Siebenthal et al.[29]
Abbreviations: FIA = fractional iron absorption, IQR = interquartile range.

A limitation of this study is that it was conducted in a purposive sample: iron-deficient, nonanemic, generally healthy young women. Furthermore, the BMI of the sample was in the low normal range. Generalization of the findings to the population at large should therefore be made with caution. Generalization to clinical populations, including special populations, such as patients with iron-deficiency anemia, pregnant or postmenopausal women, and persons with nutritional deficiencies, should also be made with caution.

Dietary Influences on the Absorption of Iron

Iron in meat-based foods is in the ferrous form in heme molecules. Iron in vegetables is in the ferric form. Ferrous iron is better absorbed than ferric iron.[30]

The acid environment in the stomach, and vitamin C in diet, help reduce ferric to ferrous iron, thereby facilitating the absorption of iron.[31] This explains why drugs that impair iron absorption include antacids, H2 receptor blockers, and proton pump inhibitors.[30]

Vitamin C improves the absorption of ferrous iron through other mechanisms, as well.[29]

Polyphenols in fruits such as berries and in beverages such as coffee and tea, phytates in plant-based foods, and casein in milk form complexes with iron, reducing its absorption.[31] Calcium supplements also impair iron absorption.[32]

Hepcidin

Hepcidin is a peptide hormone that regulates many aspects of iron homeostasis, including the absorption of iron; higher hepcidin levels are associated with lower fractional iron absorption. Hepcidin levels show diurnal variation, being higher in the afternoon than in the morning. Hepcidin levels are also increased, as a feedback mechanism, by iron administration and by rising levels of iron in blood and in the liver.[33] These observations explain why iron absorption is poorer with afternoon dosing relative to morning dosing,[29] why taking higher doses of iron are associated with lower fractional iron absorption,[34] and why at least some[35–37] but not all[38] studies find that administration of twice the daily dose on alternate days results in better fractional iron absorption and higher end point hemoglobin levels relative to daily dosing with oral iron supplements. Alternate day iron supplementation may also be better tolerated, especially in the elderly.[39]

Summary

For best absorption, oral iron supplements should be administered in the morning, on a fasting stomach, along with about 100 mg of vitamin C in the form of a tablet, or with a glass of orange or other citrus juice (which could be expected to provide about the same quantity of vitamin C). If neither vitamin C nor citrus juice is available, as the next best option, iron should be dosed with plain water. Absorption is markedly reduced if iron is administered in the afternoon, or with food such as cereals and other grains, or with beverages such as tea and coffee. Clinical messages relevant to improved absorption of oral iron supplements are presented in Box 2.

Box 2.

Clinical Messages Relevant to Improved Absorption of Oral Iron Supplements

Supplemental iron is best administered in ferrous rather than in ferric form.
Supplemental iron is best administered in the morning rather than in the afternoon.
Supplemental iron is best administered on an empty stomach (no food for at least 2 hours) rather than with food.
Subjects should ideally wait for a further hour to consume food and beverages, after ingesting iron supplements.
Supplemental iron is best administered with a low dose of vitamin C (eg, 100 mg) or with a beverage containing an equivalent quantity of vitamin C (eg, a glass of orange juice).
Supplemental iron should not be administered with foods that contain phytins (eg, plant-based foods such as cereals and other grains), polyphenols (eg, coffee and tea), casein (eg, milk), and calcium (eg, milk-based products).
Administration of supplemental iron at twice the daily dose on alternate days may result in better fractional iron absorption and quicker correction of iron-deficiency anemia than administration through daily dosing. Alternate day iron dosing may also be better tolerated, especially in the elderly.

Parting Notes

Oral iron supplements can cause constipation but less often can cause diarrhea; in the latter event, taking iron with a full meal may reduce the risk of diarrhea. The unavoidable consequence is that it will take longer to correct the iron deficiency and to replenish iron stores after the deficiency has been corrected.

Oral iron supplementation should be continued until the reason for supplementation, such as normalizing the hemoglobin level, has been addressed; subsequently, it is usual to continue supplementation for a further 3 months, or to a target ferritin level of >100 µg/L. The continuation serves to replenish iron reserves in the body, as reflected by the ferritin level.[39] Iron supplementation should not be continued beyond necessity because it can result in iron deposits in tissues and damage to organs such as the liver, heart, and pancreas. For more information, including discussions on dosing with intravenous iron, readers are referred to publicly available guidelines.[39,40] For information about how iron is handled in the body, readers may consult the review by Anderson and Frazer.[1]

As a final note, iron supplements should be ingested with plenty of fluids and with the body erect. The body should remain erect, that is, not supine, for at least 30–60 min afterwards. These two precautions reduce the risk of pill esophagitis.[41]

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