Clinician's Guide to Oral Iron

Iron Corner
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SUMMARY

- Iron deficiency, the most common cause of anemia, may be treated with oral iron supplements, or less frequently with parenteral iron.
- Since most oral iron preparations are non-prescription, physicians must provide their patients with adequate education to ensure that they are choosing the right iron, taking it at the right time, and minimizing the common side effects that can often lead to discontinuation of therapy.

Introduction

Anemia is a common medical problem that is frequently diagnosed and treated by family physicians. Iron deficiency, the most common cause of anemia, may be treated with oral iron supplements, or less frequently with parenteral iron. Supplements are especially important when an individual is experiencing clinical symptoms of iron deficiency anemia. The goal of providing oral iron supplements is to supply sufficient iron to restore normal iron stores and replenish hemoglobin deficits. Oral supplements are most cost effective and may be only form of iron in resource-poor settings. Oral supplements are usually preferred method in children and adolescents. Use of oral iron avoids need for intravenous access and a monitored infusion setting.

Doctor William Ershler, formerly a hematologist at the National Institute of Health stated, "Once a physician has determined a diagnosis of iron deficiency anemia, searching for the cause of that anemia is as important, if not more important, than correcting the anemia. Initiating a work-up to get to the cause of the diagnosis may uncover a potentially curable cancer before it progresses. Referral to a gastroenterologist or hematologist may be necessary if the etiology of the anemia is not easily detectable."

In order for oral iron therapy to effectively resolve iron deficiency anemia, patients must receive and absorb an adequate dose of elemental iron. Since most oral iron preparations are non-prescription, physicians must provide their patients with adequate education to ensure that they are choosing the right iron, taking it at the right time, and minimizing the common side effects that can often lead to discontinuation of therapy.

Over-the-Counter Iron Supplements Contain Varying Amounts of Iron (examples)

Iron Supplement	*Tablet Size*	*Elemental Iron*
Ferrous fumarate	325 mg	108 mg
Ferrous sulfate	325 mg	65 mg
Ferrous gluconate	325 mg	35 mg
Iron bisglycinate		25 mg
Iron protein succinylate	300 mg	18 mg

For adults who are not pregnant, the Centers for Disease Control and Prevention (CDC) recommends 50-60 mg of oral elemental iron twice daily for three months for the therapeutic treatment of iron deficiency anemia.[1] However, this dosing regimen has recently been questioned. Iron supplements of 60 mg Fe as $FeSO_4$ increase hepcidin for up to 24 hours and are associated with lower iron absorption on the following day.[2] The data showed that fractional absorption in iron-depleted women is highest at low iron doses (40-80 mg) and that acute, consecutive-day dosing results in decreased iron bioavailability. Twice daily supplementation seems to have limited additional effect compared with daily administration and may increase gastrointestinal side-effects. In fact, alternate-day schedules of iron administration may maximize fractional absorption, increase dosage efficacy, reduce gastrointestinal exposure to unabsorbed iron and ultimately improve tolerance of iron supplements.[3,4]

Iron Supplements

There are a large number of iron preparations available with various amounts of iron, iron salts, complexes, combinations, and dosing regimens. They are available in regular tablets and capsules, liquid and drops, coated and extended-release tablets and capsules. Oral iron preparations are available in both ferrous and ferric states. The most commonly available oral preparations include ferrous sulfate, ferrous gluconate and ferrous fumarate. All three forms are well absorbed but differ in elemental iron content. Ferrous sulfate is the

least expensive and most commonly used oral iron supplement.[6] Studies have shown that Iron bisglycinate and iron protein succinylate are associated with less gastrointestinal intolerance than ferrous sulfate, gluconate and fumarate for a comparable dose of elemental iron but are more expensive.[5]

Compliance and Effectiveness

According to Ershler, "It is very important to follow up with your patients after starting oral iron therapy. Compliance is a huge problem; many patients simply cannot take oral iron. Asking patients specific questions about how, when, and how often they take their iron therapy coupled with a laboratory work-up will help determine compliance. Patients who are unable to complete a course of oral iron can be treated with an intravenous iron agent. The newer IV irons are safe and effective and an excellent alternative for these patients."

The effectiveness of iron supplementation is determined by measuring laboratory indices, including reticulocyte count, hemoglobin and ferritin levels. The reticulocyte hemoglobin content in picograms is an early indicator of a response to iron therapy, increasing within a few days of initiating therapy. Hemoglobin usually increases within 2-3 weeks of starting iron supplementation. Therapeutic doses of iron should increase hemoglobin levels by 0.7-1.0 g/dL per week. Reticulocytosis occurs within 7-10 days after initiation of iron therapy.[7] Serum ferritin level is a more accurate measure of total body iron stores. Adequate iron replacement has typically occurred when the serum ferritin level reaches 100 µg/L. If patients with iron deficiency anemia do not begin to respond to iron supplementation within a few weeks, the patient should be re-evaluated for blood loss, noncompliance or poor absorption.

One common reason for iron therapy treatment failure is ineffective iron intake. This could be due to non-compliance, under-dosing, or a failure to absorb iron from the supplement. Iron uptake and absorption may be impaired by malabsorption states, as well as the concomitant use of medications and ingestion of foods that inhibit iron absorption.[7] Some of the factors that affect the absorption of iron supplements are listed in the next section.

Factors that Affect the Absorption of Iron Supplements

Oral iron supplements must dissolve rapidly in the stomach so that the iron can be absorbed in the duodenum or upper jejunum. Enteric-coated reparations and long-acting supplements may be ineffective, since they do not dissolve in the stomach.[5]

Ascorbic acid is an enhancer of iron absorption and can reverse the inhibiting effects of substances such as tea and calcium. Ascorbic acid facilitates iron absorption by forming a chelate with ferric iron at acid pH that remains soluble at the alkaline pH of the duodenum.[8]

To minimize side effects, iron supplements are often taken with food. This may decrease iron absorption by as much as 40-66%.[7]

Food and drug interactions may reduce the efficacy of oral iron.

The primary reason for failure of iron therapy is poor compliance, often related to the frequent gastrointestinal side effects of oral iron. In those circumstances in which ongoing comorbid conditions are absent, blood loss mitigated, and lack of significant gastrointestinal side effects manifest, oral iron is very inexpensive, safe and effective. However, a meta-analysis covering thousands of patients treated with oral iron reported an incidence of 70% of significant gastrointestinal side effects associated with decrements in adherence.[9]

Foods and Drugs that Impair Iron Absorption

- Taking oral iron with food reduces absorption
- Caffeinated beverages (especially tea)
- Calcium containing foods and beverages
- Calcium supplements
- Antacids
- H-2 receptor blockers

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Physicians can help minimize the risk of treatment failure through the proper selection and dosing of iron supplements along with educating patients on strategies to maximize iron absorption, manage side effects, and improve compliance. Effective iron supplementation can help patients to relieve the symptoms of iron deficiency anemia, improve quality of life and improve their well-being.

There is a growing body of evidence supporting superior outcomes with intravenous iron, especially in the chronic kidney disease and chronic heart failure populations. One should not hesitate to move to intravenous iron early as an alternative treatment when gastrointestinal intolerance, a poor response or non-adherence to oral iron is encountered. In many cases, one can expect an improved, faster, more convenient and less toxic outcome.[10]

Categories of Oral Iron

There is great interest in the development of compounds better tolerated than iron salts; numerous compounds have been proposed (eg, sucrosomial iron, heme iron polypeptide, iron containing nanoparticles), but studies are limited. Sucrosomial iron has been tested in patients with CKD, but the mechanism of absorption and the real benefits are uncertain. In the same condition, the phosphate binder iron ferric citrate simultaneously corrects both hyperphosphatemia and iron deficiency; its double effect is being tested in a clinical trial in CKD. A phase 3 trial of ferric maltol provided positive results on iron deficiency anemia in inflammatory bowel diseases. Rigorously designed clinical trials are needed to confirm the efficacy of these iron preparations.

Iron Salts

Ferrous sulfate, ferrous fumarate, and ferrous gluconate are the iron salt formulations most commonly prescribed for treatment of iron deficiency anemia in otherwise healthy patients, given their general availability, and low cost. However, expect a discontinuation or non-compliance rate of as high as 30-40% due to gastrointestinal side effects. In patients with co-morbid conditions associated with inflammation and an increase in hepcidin, ferrous sulfate (as well as other iron salts and, to a great degree, oral iron in general) will be ineffective. An increase in the dose of oral iron in an effort to increase absorption will only result in increased gastrointestinal toxicity.

Ferrous sulfate is generally ineffective in the immediate post-surgical setting due to post-surgical inflammation and may contribute to a prolongation in post-operative ileus.

Carbonyl Iron and Polysaccharide-iron Complex

Carbonyl iron is available in the U.S. as Feosol with Carbonyl Iron. This is not an iron salt, but rather microparticles of elemental iron. It requires an acidic environment in the stomach for the microparticles to dissolve and form a hydrochloride salt.

It does not appear to offer a significant advantage over ferrous sulfate other than less poisoning potential in children. Niferex is a polysaccharide iron complex consisting of ferric iron complexed to hydrolyzed starch. It is promoted to cause less GI irritation, but the claim is unproven.

Heme Iron

A heme iron polypeptide is commercially available and marketed in the United States as *Proferrin ES* or *Proferrin Forte* (combined with 1 mg of folate and therefore requiring a prescription). This product is made from hemoglobin extracted from cow red blood cells.

Data suggest that heme iron is better tolerated and better absorbed than iron salts. However, like other oral iron supplements, bioavailability of the iron moiety is limited in patients with inflammation and elevated hepcidin levels.

Heme iron is an excellent alternative to ferrous sulfate in otherwise healthy patients with iron deficiency, who are intolerant to iron salts. It is significantly more expensive.

Iron Amino Acid Chelates

These iron products consist of a conjugate of ferrous iron with an amino acid, typically glycine. Products marketed in the United States include *Easy Iron, Gentle Iron,* and *Ferrochel* (combined with calcium, vitamin B12, vitamin C, and folate).

There are some data suggesting higher bioavailability than iron salts in otherwise healthy, iron deficient patients. The iron amino acid chelates appear less likely to cause gastrointestinal intolerance than the iron salts and represent another (and only modestly more expensive) alternative to ferrous sulfate.

Iron Protein Succinylate (IPS)

These iron products are a form of ferric iron bound with a chemically modified protein (casein) via succinylation that stabilizes the complex. IPS is insoluble at low pH and becomes soluble in the duodenum due to hydrolysis of the protein moiety at the higher pH in the duodenum. Studies have shown a significantly lower rate of adverse events compared to ferrous fumarate, ferrous sulfate, ferrous gluconate and ferrous glycine.[11] Efficacy may be superior to the ferrous salts as well. A number of formulations are available without prescription in the United States including Ferrets IPS, Ironsorb, and Iron Protein Plus.

Novel Irons

Microencapsulated iron pyrophosphate

Microencapsulated iron pyrophosphate in liposomal form is a novel advancement in management of iron deficiency anemia. This salt is "generally recognized as safe (GRAS)" by United States Food and Drugs Administration (USFDA) Code of Federal Regulation. Furthermore, European Food Safety Authority (EFSA) has also declared iron pyrophosphate to be a safe food additive.[11,12] Comparatively to conventional oral iron salts, microencapsulated liposomal iron has the highest bioavailability. It leads to quicker increase in serum hemoglobin levels, its taste has better palatability, and it doesn't have unwanted effects such as heartburn, GI upset, and constipation.

Sucrosomial Iron Chemical

Sucrosomial iron is an oral iron preparation consisting of ferric pyrophosphate protected by a phospholipid bilayer membrane made up of primarily a sunflower lecithin.[11] Preclinical data have shown that sucrosomial iron retains the iron in the sucrosome when in stomach acid, which allows intact sucrosomes to reach the small intestine where they are absorbed. A randomized open-label trial evaluated oral sucrosomial iron in non-dialysis dependent patient with iron deficiency anemia.[13] Patients were randomized 2:1 to receive oral sucrosomial iron 30 mg/d for 3 months or IV ferrous gluconate 125 mg/wk to a total dose of 1000 mg, with follow-up of 4 months. The study indicated that short-term oral sucrosomial iron was as effective as IV ferrous gluconate at correcting anemia, with a favorable tolerability profile. Sucrosomial iron also has been evaluated in several other clinical settings, including IDA associated associated with pregnancy, inflammatory bowel disease, celiac disease, cancer, and bleeding.[13,14]

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