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Treatment of Iron Deficiency in Gastroenterology: A New Paradigm

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Iron deficiency is the most common micronutrient deficiency in the world and complicates a host of gastrointestinal maladies associated with blood loss. Oral iron, the frontline standard, is often poorly tolerated and ineffective. Oral iron may also cause injury to gastrointestinal epithelium and has been shown to negatively impact the gut microbiome. Newer formulations of intravenous iron have been to shown to be effective with a similar safely profile to placebo. These formulations contain complex carbohydrates that bind elemental iron more tightly, allowing a complete replacement dose to be administered in a single office visit of 15-60 minutes. Total dose infusion of intravenous iron improves convenience for both physician and patient and decreases the overall cost of care. There is now ample evidence to move intravenous iron to the frontline in all gastrointestinal disorders in which oral iron is ineffective, and should be the preferred route of administration when oral iron intolerance occurs.

INTRODUCTION

Iron deficiency is recognized as the most common micronutrient deficiency, estimated to affect more than 35% of the world's population.[1] Cells with the greatest ability to absorb iron are found in the distal duodenum and proximal jejunum. Patients with GI disease or surgical resections affecting these areas are at high risk for iron deficiency. Bleeding is a common manifestation of many GI disorders, and subsequently iron deficiency, with or without anemia, is a frequent comorbidity.

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Iron Absorption

Iron, in the presence of gastric acid, is conjugated to vitamin C, amino acids, and sugars, which protect it from the alkaline secretions of the pancreas, which are necessary for normal digestion. Absent that event, the iron is converted to ferric hydroxide (rust), which is unabsorbable from the GI tract. Dietary iron is best taken on an empty stomach, which allows the gastric acid to promote binding, and is then absorbed in the duodenum and

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proximal jejunum. Iron homoeostasis is regulated by the protein hepcidin, which has a crucial role in iron availability to tissues by blocking both absorption at the level of the intestinal epithelium and iron release from circulating macrophages. This regulation is mediated by hepcidin's ability to irreversibly inactivate ferroportin-1 (FPN1), the only known iron export protein in humans.[2] The inactivation of ferroportin by hepcidin results in decreased absorption and subsequent failure of the intracellular iron to be loaded on to transferrin for subsequent erythropoiesis. Circulating macrophages, a reservoir for iron, are similarly expressed with ferroportin with similar loss of the function of iron export in the presence of hepcidin. Subsequently, high expression of hepcidin (due to inflammation and other co-morbid conditions, oral iron supplementation, iron sufficiency) decreases plasma iron concentrations; low expression (due to iron deficiency, hemochromatosis) increases plasma iron concentrations.

Disease States Altering Iron Absorption

A number of frequently occurring GI disorders may impair iron absorption (Table 1). *Helicobacter pylori* may cause iron malabsorption by causing atrophic gastritis, resulting in reduced soluble iron for absorption from acid insufficiency.[3] Long term use of high dose proton pump inhibitors (PPIs) and autoimmune atrophic gastritis may also contribute to iron deficiency through a similar mechanism.[4,5]

After roux en y gastric bypass, the blind loop (consisting of distal stomach, duodenum and proximal jejunum) is bypassed. As a result, oral iron is not available for absorption, precipitating iron deficiency in the majority of patients despite oral supplementation.[6] Patients with gastric bypass may also have diet alterations as well as a reduction in gastric acid, both of which contribute to iron deficiency.[7,8] Celiac disease can cause duodenal inflammation resulting in iron malabsorption and resulting deficiency.[9] Iron deficiency with inflammatory bowel disease (IBD), in addition to bleeding, is exacerbated by inflammation in the small bowel with malabsorption and the chronic inflammatory state associated with the disease.[10,11] Early on, dietary iron may provide enough iron to maintain normal hemoglobin concentrations as iron stores are depleted. As a result, iron deficiency is often present without anemia, but may result in symptoms of fatigue, decreased exercise tolerance, pagophagia (ice craving), or other forms of pica, and restless leg syndrome.

Table 1. GI Conditions Commonly Associated with Iron Deficiency

- Erosive esophagitis/gastritis
- Peptic ulcer disease
- Gastrointestinal angiodysplasia
- Gastrointestinal malignancy
- Inflammatory bowel disease due to:
  - Inflammation in the small bowel with malabsorption
  - Chronic blood loss
  - Chronic inflammatory state
- Celiac disease *Helicobacter pylori*
- *Helicobacter pylori*
- Gastric bypass, or any other surgery where the duodenum and proximal jejunum are bypassed
- Atrophic gastritis

ORAL IRON SUPPLEMENTATION

It was in 1681 when Sydenham first used iron filings in cold wine to treat the symptoms of the 'green sickness',[12] later termed chlorosis by Pierre Blaud. It was not long thereafter that oral iron was used to treat patients with wounds during the American Civil war. Today, iron deficiency is the most common micronutrient deficiency on the planet, and oral iron remains frontline therapy for most conditions. The advantages of oral iron are that it is readily available, inexpensive, convenient, and noninvasive. Unfortunately, significant GI side effects frequently occur, which often leads to poor adherence. A recent meta-analysis of prospective studies comparing oral ferrous sulfate to placebo and parenteral iron found more than 70% of patients reported significant GI toxicity with oral iron, including nausea, abdominal pain, diarrhea, and constipation.[14]

While several oral iron preparations have been marketed with claims of superiority in either tolerability or efficacy, none have been shown in prospective studies to be superior to ferrous sulfate[15,16] (Table 2). Oral formulations with slow release of iron and those with enteric coating may result in better GI tolerance, but are released beyond the duodenum and proximal jejunum (primary site for iron absorption). This results in a lack of adequate GI absorption, and thus these formulations should not be prescribed due to their lack of clinical efficacy.[15] Studies have shown that oral dosing of iron upregulates hepcidin levels, leading to impairment of intestinal iron absorption.[17] Absorption of oral iron tablets decreases when taken daily or twice daily, compared to alternate day therapy,[18] thus alternate day dosing of oral iron may be a preferable dosing regimen.

Inflammatory Bowel Disease

Although oral iron is commonly prescribed to treat iron deficiency in patients with IBD, several studies have shown it is not appropriate in the setting of active disease. Oral iron has been shown to exacerbate intestinal inflammation of IBD independent of anemia,[19] and cause luminal changes in microbiota and bacterial metabolism, which may negatively alter the microbiome.[20,21] Studies have also found response to oral iron therapy depends on levels of C-reactive protein (CRP), with high CRP levels correlating with weaker hemoglobin response.[22] Thus, iron should only be given orally to IBD patients with inactive disease, mild anemia, and good tolerance of oral iron; in patients with active IBD oral iron should be avoided. One new oral iron formulation, ferric maltol, has been studied in patients with inactive IBD and was found to be more effective at correcting anemia compared to placebo and did not appear to exacerbate IBD activity.[23] This formulation was recently approved by the FDA and appears to be a promising option for this population.

Other GI Disease States

Tolerance of oral iron in other GI diseases is also problematic. In patients with upper GI tract disorders such as erosive esophagitis and peptic ulcer disease, oral iron may exacerbate luminal symptoms leading to patient nonadherence.

Table 2. Common Oral Iron Preparations

- Carbonyl iron (iron pentacarbonyl)
- Ferric citrate
- Ferric maltol *
- Ferrous ascorbate
- Ferrous chloride**
- Ferrous fumarate
- Ferrous gluconate
- Ferrous succinate**
- Ferrous sulfate
- Ferrous sulfate anhydrous
- Polysaccharide-iron complex

** Approved by FDA July 2019*
*** Not routinely available in US*

Patients with GI motility disorders and small intestinal bacterial overgrowth have symptoms of bloating, abdominal discomfort and altered bowel habits.[24] As a result, this population also does not tolerate oral iron well. Finally, strong evidence supports avoidance of oral iron after gastric bypass and with ongoing active blood loss.[15,25]

INTRAVENOUS IRON

In the past, many clinicians were taught that intravenous iron was dangerous; much of this misperception stems from the early use of colloidal ferric hydroxide and high molecular weight iron dextran, both of which were associated with toxicity and neither of which are available today.[26] In 1954, a solution of iron dextran was introduced by Baird and Padmore for the treatment of iron deficiency by the intramuscular route.[27] This painful method of administration, which was neither safer, nor more efficacious than the IV route, gained little enthusiasm among clinicians. In the next two decades it became clear that the administration of parenteral iron by the IV route was better tolerated, easier to administer, and most importantly, more safe.[28-30] Nonetheless, IV iron remained a relatively minor product, used in situations where there was an urgent need for iron replacement and oral iron

Table 3. Cost of Available IV Iron Formulations*

Formulation	Cost/gram
LMW iron dextran (INFeD®)	$245.00
Ferric gluconate (Ferrlecit®)	$1000.00
Iron sucrose (Venofer®)	$500.00
Ferumoxytol (Feraheme®)	$932.00 (vial size 510 mg at $466 /vial)
Ferric carboxymaltose (Injectafer®)	$1112.00 (vial size 750mg at $834.00/vial)

**2019 acquisition costs, Auerbach Hematology and Oncology*

could not be tolerated. Today there is a much greater appreciation of the role of IV iron across a large number of diagnoses associated with iron deficiency.

Currently there are five IV iron formulations available in the U.S. (Table 3). Two of these, iron sucrose (Venofer®) and ferric gluconate (Ferrlecit®), have increased labile free iron after an injection which limits the amount that can be infused during a single session.[31] These formulations are reasonable options for hemodialysis patients in whom frequent visits are necessary, but as they require multiple visits to an infusion center, they are not as convenient as other formulations that may be given as a single or total dose infusion.

The oldest of the formulations able to be administered as a total dose infusion (TDI) is low molecular weight iron dextran (INFeD®). The method of administration approved by the FDA is 100mg per infusion; however, a TDI of one gram over one hour has been shown to be superior to this regimen.[32] In one study, 1288 infusions of iron dextran were administered to 888 patients, with hemoglobin and hematopoietic response (> 2 grams) achieved in 90% of patients with no serious adverse events observed. Compared to the FDA approved method of administration, TDI is less expensive, decreases the chances for minor infusion reactions (observed with all of the formulations), and extravasation risk, and finally, is more convenient for patients and practitioners.[33] The second of the formulations approved as a TDI is ferumoxytol (Feraheme®). Ferumoxytol is approved for a 510 mg infusion in 15 minutes. However, equal safety and efficacy of a single 1020mg infusion in 15-30 minutes has been demonstrated.[32] Some insurance plans pay for this method of administration, but others do not, which limits the routine administration of the higher dose. Ferumoxytol has been shown to be effective and safe across a broad spectrum of diagnoses. Ferumoxytol has been compared to iron sucrose[34] and ferric carboxymaltose[35] and has been shown to be equally safe and effective. Ferumoxytol is also paramagnetic and has been used as an off-label MRI contrast agent. If an MRI is planned, the radiologist should be notified of the use of ferumoxytol and gadolinium avoided.

The third formulation approved as a TDI in the United States is ferric carboxymaltose (FCM; Injectafer®). The FDA approved method of administration is 750 mg given over 15 minutes, but studies in Europe have reported the safety and effectiveness of 1000 mg administered over 15 minutes.[36] In the United States the only vial size available is 750mg, requiring two visits to administer this dose. While it is possible that 1500mg may offer an advantage, in comparison to ferumoxytol, 1500mg of FCM (two vials) was compared to 1020mg of ferumoxytol (two vials) and at five weeks the differences in hemoglobin response were not clinically significant.[35] FCM has been shown to be safe and effective in IBD and has been shown to prevent recurrence of anemia, even in patients with active disease.[37] FCM has also been compared to oral iron in IBD and shown to be more effective, significantly better tolerated with less toxicity.[38] Of note, FCM has been associated with hypophosphatemia in more

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than 50% of patients to whom it is administered,[39] and cases of symptomatic hypophosphatemia have been reported with this agent.[40,41] Serum phosphate should be monitored during and after treatment with FCM, and this formulation should be avoided in patients with documented hypophosphatemia (or are at risk for, or actively refeeding).

The fourth formulation that may be administered as a TDI is iron isomaltoside (Monofer®), currently available only in Europe. As with other formulations, isomaltoside has been shown to be safe and effective across a similar population with iron deficiency.[42,43] Isomaltoside has also been shown to have a very low incidence of hypophosphatemia.

SAFETY OF INTRAVENOUS IRON

While intravenous iron has been shown to be quite safe, there remains a risk of minor infusion reactions due to labile free iron, which occur in 1-3% of administrations. In a recent meta-analysis, the results of more than 10,000 patients who were treated with intravenous iron were reported.[44] Compared to oral iron, placebo, and even intramuscular iron (which should never be given), while minor infusion reactions were observed with IV iron, there was no increase in serious adverse events compared to any comparator including placebo. A marked reduction in GI toxicity was reported with IV iron compared to oral iron. Minor infusion reactions typically are self- limited and consist of pressure in the chest or back, or flushing in the face. Notably there is no tachypnea, tachycardia, hypotension, wheezing, stridor or periorbital edema, and the risk of anaphylaxis is very rare. Inappropriate intervention with antihistamines or vasopressors, which are known to cause hypotension, tachycardia, diaphoresis, and somnolence, may convert minor infusion reactions to more serious adverse events. Premedication with antihistamines should be discouraged, although premedication with steroids may decrease the likelihood of minor infusion reactions in those with significant allergic diatheses or prior history of reaction (125mg of methylprednisolone and 50mg of ranitidine or famotidine in patients with more than one drug allergy or asthma or prior minor infusion reaction).

CONCLUSION

Iron deficiency is of global consequence, and patients with gastrointestinal disease are at a heightened risk due to alterations in absorption and increased blood loss. Based on the preponderance of published evidence, the use of oral iron should be discouraged in patients with IBD. In patients who have undergone bariatric surgery or other surgical resection that bypasses the duodenum, oral iron is poorly absorbed and largely ineffective hence, it should also be avoided. For those with GI tract angiodysplasia, oral iron typically cannot keep up with blood loss and IV iron is preferred over oral formulations. Whereas there may be a benefit with oral iron supplementation in other diseases of the GI tract, GI intolerance is common and IV iron typically simplifies care.

It is reasonable to recommend oral iron for those patients with inactive disease and good tolerance of oral iron. Until prospective data are available comparing daily or alternate day dosing, we feel that alternate day dosing of oral iron is advisable. If oral iron intolerance or ineffectiveness is observed, switching to the IV route is prudent.

Clinicians should familiarize themselves with the available options for iron repletion in GI disease. Based on current evidence, IV iron administration should be moved forward in the treatment paradigm of iron deficiency anemia. ■

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