Parenteral Iron Therapy

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Iron is an essential component of hemoglobin and myoglobin and of many enzymes involved in redox reactions and energy metabolism. It plays a valuable role in the transport and storage of oxygen and oxidative metabolism, and in cell growth and proliferation. Most of the iron in plasma is destined for erythropoiesis in the bone marrow. Dietary iron absorption in the duodenum is a complex process under control of several proteins, and is influenced by iron requirement, iron concentration in the intestinal lumen and the integrity of the cellular wall anatomy.

Iron deficiency is a leading cause of anemia, affecting over one-half billion people worldwide. Blood loss is almost invariably the culprit of iron deficiency in adults. The high demand for iron created by neonatal and adolescent growth spurts occasionally produces iron deficiency in children. Iron deficiency may result from abnormal iron uptake from the gastrointestinal tract, either due to poor bioavailability that may be modified by high gastric pH (hemigastrectomy, vagotomy, pernicious anemia, histamine H2 receptor blockers, calcium-based antacids), disruption of intestinal structure (Crohn's disease, celiac disease), and presence of inhibitors (phylates, tannins, soil clay, laundry starch, iron overload). Blood loss is the world's leading cause of iron deficiency. The gastrointestinal tract is both the site of iron uptake and the most common site of blood loss. The gastrointestinal tract is unrivalled as a potential site of occult blood loss. The most frequent congenital defects in the gastrointestinal tract are Meckel's diverticulum, persistent omphalomesenteric duct, colonic arteriovenous malformations. Other acquired causes are peptic ulcer disease, gastric hiatal hernia, milk-induced enteropathy, parasitic infestation, and H*elicobacter pylori* infection. The latter infection has been postulated to cause refractory iron deficiency by suppression of acid secretion through induction of interleukin-1-beta and tumor necrosis factor-alpha that are potent inhibitors of gastric parietal cell function, and by induction of autoimmune gastritis [1,2].

Depletion of iron stores precedes impaired production of iron-containing proteins, the most prominent of which is hemoglobin. The two key stages of iron deficiency are depletion of iron stores without anemia, and depletion of iron stores with anemia [3].

In the last ten years a plethora of knowledge on the molecular control of iron has been accumulated. The journey starts in the duodenal enterocyte with the binding of iron to transferin receptor, forming specialized endosomes, releasing the iron through the activity of divalent metal transporter. Some iron is stored in the cell in ferritin, and the remainder must pass through the basolateral membrane to reach the plasma. This is carried out by a joint action of an iron exporter, ferroportin 1 and hephesin, a possible ferroxidase [4-6]. The former proteins are under tight control of hepcidin, considered a key regulator of iron metabolism. In excess iron state, hepcidin mRNA over-expression and high hepcidin level inhibit duodenal iron absorption. It is postulated that iron-sensing in the gut may lead to a cross-talk with hepatocytes and macrophages and regulate hepcidin production [7]. Inappropriate expression of hepcidin is associated with iron refractory anemia, mainly in anemias of chronic diseases, where partial hepcidin deficiency may contribute to iron overload in, most commonly, hemochromatosis [8].

Malignancy of the gastrointestinal tract is the haunting specter in adults with iron deficiency. In children, iron deficiency due to growth spurts, poor dietary patterns, or benign gastrointestinal bleeding sources are much more common. After the cause of the iron deficiency has been ascertained, oral iron supplementation replaces stores most efficiently. Oral iron supplementation is the ideal way to replace iron stores as it uses the body's normal mechanisms. The shortcoming is the gastrointestinal tract's limited capacity for iron absorption. Only about 2–3 mg of elemental iron is absorbed, even when 50 or 100 mg are presented to the gut lumen. Most orally consumed iron flows untouched through the alimentary tract. Replenishing a 2000 mg iron deficit can take most of a year. With ongoing blood loss, replacement of stores with oral iron becomes a nearly impossible task. Although ferrous sulphate is often recommended to treat iron deficiency, frequent problems with the drug – including gastrointestinal discomfort, bloating and other distress – make it unacceptable to many patients. Ferrous gluconate produces fewer problems, and is preferable as the initial treatment of iron deficiency. Ascorbic acid supplementation enhances iron absorption. Polysaccharide-iron complex, a replacement form of iron that differs from the iron salts, is a more recent option. The polar oxygen groups in the polysaccharide form coordination complexes with the iron atoms. The well-hydrated microspheres of polysaccharide iron remain in solution over a wide pH range. Most patients tolerate this form of iron better than the iron salts, however no study has compared iron uptake from polysaccharide-iron complex and ferric salts.

Many, if not most, patients fail to comply with such a pro-

longed medical regimen. Therapeutic failures are common with oral iron replacement. There are conditions where dietary iron intake is adequate but iron absorption, recycling and distribution from iron stores are insufficient to meet the needs of hemoglobin synthesis in the bone marrow. This "iron refractory anemia" may represent anemia of inflammation as well as those not responding to oral iron supplementation. For these patients intravenous iron therapy is the preferred treatment.

In this issue of *IMAJ*, Pinsk and co-authors [9] report the efficacy and safety of intravenous iron sucrose therapy in 45 children with iron deficiency anemia caused by various conditions. They observed excellent tolerance, low profile adverse reactions and, most important, a rapid rise of hemoglobin concentration. There are concerns about the release of free iron during intravenous iron infusions because the capacity of available apotransferrin to bind the free iron can be exceeded. Free iron is known to increase the toxicity of free radicals and other reactive oxygen products that are normally found in the body, thus it contributes to oxidative stress. Trace amounts of free iron can catalyse production of a highly toxic hydroxyl radical via Fenton/Haber-Weiss reaction cycle. The risk of inducing the release of free iron appears to depend on the dose of intravenous iron, the rate of iron infusion, and the available apotransferrin/transferrin to bind the iron. Many of the adverse events attributed to sodium ferric gluconate – including flushing, hypotension, nausea, vomiting and diarrhea – have been linked with the release of free iron [10]. Van Wyck et al. [11] report that regardless of the increasing use of intravenous iron, the availability of safe carbohydrate-iron colloid complexes eliminated most of the side effects, and more important, no intravenous iron compound generated detectable free iron, but labile iron without potential adverse effect.

It is not yet determined for how long one should be treated with oral iron supplementation before being defined non-compliant or resistant and switched to intravenous therapy. In a randomized controlled trial, anemic women were assigned within 10 days postpartum to receive either intraveous ferric carboxymaltose or ferrous sulfate (FeSO4) 325 mg orally three times daily for 6 weeks [12]. Pinsk et al. [9] treated their patients with a therapeutic dose of 6 mg/kg for 3 months without effect on hemoglobin value and red blood cell indices. In the context of iron refractory anemia it is probably reasonable to withhold intravenous therapy for at least 3 months, with a close follow-up of laboratory values.

Although there are no reliable diagnostic tests to discriminate between absorber and non-absorber, there are only a few reports on the value of iron absorption test [13,14]. It is suggested that a flat absorption curve indicates an abnormal and decreased absorption capacity, necessitating intravenous supplementation that bypasses the gastrointestinal tract.

Recently, Finberg and colleagues [15] showed that mutations in TMPRSS6, which encodes a type II transmembrane serine protease by the liver, cause iron refractory anemia in humans by interfering with regulation of hepcidin expression. The application of new molecular tests for the analysis of mutations and single nucleotide polymorphisms in the increasing number of genes participating in the control of iron metabolism will allow a more rapid and distinctive diagnosis of iron deficiency states, and may point to the non-absorber who requires earlier intravenous iron therapy.

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