Iron Deficiency: When and Why Oral Iron May Not Be Enough

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Abstract
Use of intravenous iron in children has been limited due to concerns regarding adverse effects. However, newer preparations of intravenous iron have been shown to be effective and associated with fewer side effects in adults as well as in preliminary studies involving children. Indications for intravenous iron might include iron deficiency secondary to dietary causes, blood loss unresponsive to oral iron and situations where oral iron is ineffective, contraindicated or when functional iron deficiency exists. This review will discuss the various preparations of iron available for parenteral administration and the potential indications for their use in children.

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Overview of Iron Deficiency

Prevalence and Etiology

Iron deficiency is the most common mineral deficiency in the world, affecting both high income and developing countries. For example, its prevalence in the United States is highest in toddlers and adolescent females, with rates of 9–14% in both groups [1]. Iron deficiency results from several distinct etiologies with varying prevalence dependent primarily on age. It may be a consequence of inadequate iron endowment at birth. This is usually due to low birth weight and occurs with increased frequency in developing countries where malnutrition is prevalent. Decreased iron intake is most common in infants and young children and results primarily from excessive cow’s milk intake, which causes anemia by three primary mechanisms: (1) deficiency of bioavailable iron, (2) microvascular gastrointestinal blood loss when consumed in large quantities, and (3) inhibited duodenal absorption of nonheme iron contained in other foods [2]. Another prevalent etiology for iron deficiency in developed countries
is excessive blood loss. This is primarily seen in adolescent, menstruating females but also may occur as a result of recurrent epistaxis or gastrointestinal bleeding accompanying inflammatory bowel disease (IBD) or other anatomic lesions. In low-income tropical countries parasitic infection, most commonly hookworm infestation, is frequently responsible for chronic intestinal bleeding. Rarely, iron deficiency in young patients presents with malabsorption resulting from anatomic, inflammatory or inherited conditions such as defects in the \textit{TMPRSS6} gene. Hereditary hemorrhagic telangiectasia can result in iron deficiency anemia due to recurrent bleeding from mucosal telangiectases or visceral arteriovenous malformations. Iron restricted erythropoiesis or functional iron deficiency, due to disordered iron homeostasis, is yet another indication for iron replacement. This may occur secondary to subacute or chronic inflammatory conditions such as cancer, infections, and autoimmune diseases as well as in patients with chronic renal failure receiving dialysis.

\textit{Overview of Iron Absorption}

Iron is primarily absorbed from the duodenum in the form of the \textit{Fe}^{2+} (ferrous) ion or as iron bound to heme. Once either form of iron enters the enterocyte, it is transported by ferroportin across its basolateral membrane and released into the circulation bound by transferrin and carried to sites where the iron will be stored or utilized. The amount of iron absorbed is closely regulated to be equivalent to that which is lost. Iron absorption is increased if iron stores are low (e.g. iron deficiency), with hypoxemia, increased erythropoietic activity, or anemia. Hepcidin is the main regulator of iron absorption. In states of iron deficiency, hypoxia, or anemia, production of hepcidin is downregulated and the transferrin receptor upregulated, thus promoting absorption of iron and utilization of iron stored in macrophages. However, with iron-restricted erythropoiesis, such as occurs with anemia of inflammation, increased production of hepcidin is stimulated by inflammatory cytokines. By subsequently binding to ferroportin it effectively blocks iron absorption from enterocytes and release from macrophages. In addition, erythropoietin production is suppressed relative to the degree of anemia present. Similar mechanisms underlie anemia of chronic renal disease. Erythropoiesis-stimulating agents (ESA) have thus been utilized to treat iron-restricted erythropoiesis, and recent studies have also shown a possible role for parenteral iron replacement in these conditions [3].

\textit{Consequences of Iron Deficiency}

Iron deficiency is a multisystem disorder which primarily causes anemia and its accompanying clinical sequelae, but cognitive and neurologic deficits are also prevalent. Iron is required for the growth of all cells and plays a particularly important role in
the central nervous system, including neuronal and glial metabolism, myelination and production of neurotransmitters [4]. Iron deficiency may cause pica (and accordingly may contribute to increased lead burden), seizures, and, especially when present in children <2 years of age, long-lasting, irreversible neurocognitive and behavioral consequences [5, 6]. Therefore, it is imperative that iron deficiency, if not prevented, is promptly diagnosed and fully treated. The most important strategies for the prevention of iron deficiency in young children are breast feeding (with provision of iron supplements after 5–6 months of age) and avoidance of cow’s milk until beyond 1 year of age and subsequent limitation of its intake to less than or equal to 24 ounces (680 ml) daily.

**Oral Iron Therapy**

Oral iron replacement has been the longstanding treatment of choice for iron deficiency due to inadequate dietary intake or chronic blood loss. Dozens of formulations of oral iron exist but no definitive studies have ever compared the different brands or formulations for efficacy or tolerability. Generally, 3–6 mg/kg/day of elemental iron in divided doses is recommended for successful treatment of moderate-to-severe iron deficiency [7]. This approach is frequently associated with gastrointestinal side effects (such as nausea, constipation and abdominal discomfort), thus limiting adherence to the prescribed treatment course required to treat the anemia and subsequently replete iron stores [8]. In addition, in patients with ongoing blood loss, oral dosing may not provide sufficient iron to overcome the amount that is lost. Patients with malabsorption or functional iron deficiency will also not adequately respond to oral iron. Thus, there are many limitations to the success of oral iron therapy in children of all ages.

**Intravenous Iron Therapy**

**History of Intravenous Iron**

The first widely accepted parenteral iron preparation was iron dextran, introduced in the United States in 1954. Until 1992, high-molecular-weight iron dextran (HMWID) (Imferon®, Fisons, UK) was the only parenteral iron formulation available. Due to multiple reports of anaphylactic reactions with this product its use was restricted; many hematologists became apprehensive about the use of intravenous iron in general. Intramuscular Imferon® was in vogue for a while, but the repeated deep buttock injections were painful and the local skin discoloration was problematic. Accordingly, distribution of Imferon was ultimately discontinued in 1992 but was replaced by Dexferrum® (American Regent, Shirley, N.Y., USA), a similar
HMWID preparation, in 1996. Meanwhile, INFeD® (Watson Pharma, Inc., Morris-town, N.J., USA), a low-molecular-weight iron dextran (LMWID) associated with far fewer adverse reactions than HMWID was approved for use in the United States in 1991 [9, 10].

As the worldwide requirements for intravenous iron preparations increased, primarily due to the rise in the use of ESA in patients with chronic kidney disease, non-dextran intravenous irons were introduced to the market, including ferric gluconate (Ferrlecit®, Sanofi-Aventis, Paris) in 1999 and iron sucrose (Venofer®, American Regent, Shirley, N.Y., USA) shortly thereafter. These agents have since replaced iron dextran in most dialysis centers due to their perceived improved safety profile [9]. Iron sucrose has also been safely used in children with iron deficiency anemia [11, 12]. A recent study of its use in a diverse group of children without chronic renal failure for whom oral iron was unsuitable or inadequate showed encouraging results [12]. The newest intravenous iron product available on the US market, FDA approved in 2009 and EMA approved in 2012, is ferumoxytol (Feraheme®, Rienso® (EU), AMAG, Lexington, Mass., USA), which was initially designed as a novel imaging contrast agent and has been licensed for the treatment of iron deficiency anemia in adult patients with chronic kidney disease. In Europe, two additional new products have recently been approved, ferric carboxymaltose (Ferinject®, Vifor, Switzerland) and iron isomaltoside 1,000 (Monofer®, Pharmacosmos, Denmark). Both have been heralded as promising improved safety profiles and ease of dosing although currently Ferinject is only licensed for those 14 years and over and Monofer is not licensed for use in children.

Safety of Intravenous Iron Preparations

Most of the available literature comparing the efficacy and safety profiles of various intravenous iron preparations focuses on adults with chronic kidney disease. Although LMWID has a similar but more favorable side effect profile than HMWID which is associated with more serious adverse events, allergic and anaphylactic reactions can occur with both formulations [9, 13] (table 1). For example, direct comparison in 156 adults undergoing dialysis revealed a 3.5% rate of adverse effects with LMWID versus 28.6% with HMWID [14]. Many studies reporting high rates of adverse events with iron dextran do not differentiate between the two forms (HMW vs. LMW), but most reactions were likely related to the former [15]. Almost no clinical trials have yet included children without chronic kidney disease, but two recent studies of children with iron deficiency anemia of various non-renal causes showed that iron sucrose can be safely administered in an outpatient setting with good efficacy [11, 12]. A study of single total dose infusions (rather than repeated dosing) of iron dextran in children with IBD and iron deficiency confirmed its efficacy. Eleven adverse reactions occurred during 119 infusions, but it is unclear whether a LMW or HMW
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ID was responsible as both formulations were employed in study patients [16]. Total dose infusion of LMW ID has been shown to be effective in a separate study of 31 pediatric patients treated in an outpatient hematology clinic, with minor adverse reactions noted in 9 patients but no anaphylaxis or other serious adverse events [17]. Frequently patients will complain of arthralgia and myalgia during the test dose or subsequent infusion of LMW ID. However, this is generally self-limiting and does not portend more serious reactions, and most patients can successfully receive the complete infusion [18, 19].

The introduction of second-generation intravenous iron formulations, such as iron sucrose and ferric gluconate preparations are effective in the treatment of IDA and are not associated with the serious allergic reactions encountered with intravenous iron dextran. They have favorable safety profiles when compared with the dextran preparations (table 1) but at doses greater than 300 mg patients may experience transient side effects such as hypotension, abdominal pain and nausea/vomiting [20]. These dose-dependent adverse effects are thought to be vasoactive reactions due to circulating free (unbound) iron that occur when transferrin becomes temporarily oversaturated during the infusion. This problem likely results from nondextran iron preparations binding iron less tightly than dextran [20, 21]. Ferumoxytol use in children has been limited, but a preliminary report in 6 children with gastrointestinal disorders supported its safety with doses up to 12 mg/kg (maximum 510 mg, the vial content) given over 15–60 min [22].

Choice of Intravenous Iron Formulation

The selection of intravenous iron preparations will depend on the underlying indication for iron and the clinical setting (table 2). For children with renal failure undergoing dialysis, frequent small doses of a product such as ferric gluconate or iron sucrose would be a good choice given the larger experience with these products and their fa-