Use of Ferric Carboxymaltose in the Treatment of Pediatric Iron Deficiency
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While intravenous (IV) iron products have been available in the United States for more than 50 years, their use has been limited by concerns over their toxicity. All parenteral iron products are colloids of iron-carbohydrate complexes. High molecular weight iron dextran, the first product to enter the market, was associated with a significant risk for serious hypersensitivity reactions, including anaphylaxis, and was subsequently taken off the market. The first low molecular weight iron dextran products became available in the early 1990s. These formulations produce fewer serious adverse reactions, but the risk for anaphylaxis is still present.

Ferric gluconate and iron sucrose became available at the end of the 1990s as alternatives to the dextran products. While these agents further reduced the risk for adverse reactions, they bind iron less tightly than other iron products, resulting in more labile free iron after administration and limiting the dose that can be given without producing toxicity. As a result, these two products require multiple injections to provide the patient’s total dose.

Ferumoxytol, a superparamagnetic iron oxide coated with a polyglucose sorbitol carboxymethylether shell, was approved by the Food and Drug Administration (FDA) in 2009. This product produces an effective rise in hemoglobin and transferrin levels in only two doses, compared to 5 doses of iron sucrose. The hypotension reported in the first years after its approval has been minimized by lengthening the infusion time. Ferumoxytol, like the low molecular weight dextran products, carries a black box warning for hypersensitivity reactions, but the risk has been shown to be lower than that seen with the dextran formulations.

Ferric carboxymaltose (FCM) has a complex carbohydrate shell that tightly binds elemental iron and, as a result, can be given in larger doses via slow IV push or infused over 15 minutes. It was approved in Europe in 2007 and by the FDA in 2013 for use in adults with an intolerance of or inadequate response to oral iron therapy and in patients with iron deficiency associated with nondialysis-dependent chronic kidney disease. It has also been shown to be beneficial in the treatment of iron deficiency associated with cancer, chronic heart failure, and inflammatory bowel disease. A meta-analysis of five randomized, controlled trials published in March 2017 issue of *Alimentary Pharmacology and Therapeutics,* found FCM to be the most effective IV iron formulation, followed by iron sucrose. It was also determined to be better tolerated than the other products. The primary advantage of FCM over the other iron products, however, is the ability to give up to 1,000 mg as a single dose in adults, which would require ten doses of iron dextran, eight doses of ferric gluconate, five doses of iron sucrose, or two doses of ferumoxytol.

While FCM is currently not approved for use in children, recently published clinical trials have described its use in the pediatric population. Studies being conducted by the manufacturer suggest that it may be under consideration for pediatric indication in the future.

**Mechanism of Action**
Ferric carboxymaltose is a colloidal iron hydroxide-carboxymaltose complex. This formulation isolates the iron from the plasma until the complex is phagocytized by reticuloendothelial system macrophages in the liver, spleen and bone marrow. The iron is then released into an intracellular storage iron pool or taken up by transferrin to be made available for hemoglobin synthesis.

Uptake of radio-labeled iron by red blood cells ranged from 91% to 99% 24 days after a dose of FCM in adults with iron deficiency and from 61% to 84% in adults with anemia associated with renal disease. Similar uptake has been...
Laass and colleagues published the first pediatric study of FCM in 2014. This retrospective study included 72 children and adolescents between 11 months and 18 years of age (mean 12.7 years) with gastrointestinal diseases leading to iron deficiency anemia. Forty percent of the patients had Crohn’s disease and another 30% had ulcerative colitis. The median single dose was 500 mg (approximately 12 mg/kg), with a minimum dose of 50 mg and a maximum of 1,000 mg. The mean number of doses per patient was 2 ± 1.75, with a mean cumulative dose of 821 ± 203 mg. Fifty-four percent of the patients required just a single dose. Mean hemoglobin increased from 9.5 g/dL at baseline to 11.9 g/dL at the follow-up visit 9-12 weeks post-dose. Serum transferrin and transferrin saturation increased to goal by the follow-up visit during weeks 2-8. White blood cell count, platelet count, and C-reactive protein decreased during treatment, which the authors suggested may indicate a reduction in inflammation resulting from iron deficiency. Three patients experienced adverse effects; two had mild urticaria and the third had edema of the palms and fingers. There were no reports of clinically significant hypophosphatemia.

The retrospective study of both FCM and iron sucrose use in pediatric patients with Crohn’s disease was published by Valério de Azevedo and colleagues in the January 2017 issue of the Scandinavian Journal of Gastroenterology. A total of 19 children and adolescents (mean age 15.5 years) with mild disease were included in the analysis. Mean hemoglobin at baseline was 10.5 g/dL, with a mean ferritin of 20.1 mcg/L and transferrin saturation of 6%. The median total iron dose was 811.5 mg in the patients given FCM and 672.6 mg those receiving iron sucrose. The median hemoglobin at the 4-6 weeks follow-up visit had risen to 13.1 g/dL in the FCM group and 12.3 g/dL in the iron sucrose group. Six patients (four given FCM and two given iron sucrose) eventually required retreatment, with a median time to the second course of 15.5 months (range 2-25 months). No serious adverse effects were noted. The authors concluded that both drugs were acceptable treatment options in children and adolescents with Crohn’s disease.

In that same month, Powers and colleagues published a retrospective study of children treated with FCM at Children’s Medical Center in Dallas in The Journal of Pediatrics. Seventy-two patients between 9 months to 18 years of age (median 13.7 years) with iron deficiency anemia refractory to oral iron supplementation were included in the analysis. The median calculated iron deficit was 435 mg. Indications for treatment included heavy menstrual bleeding (41%), gastrointestinal disease (32%), and inadequate oral iron intake (26%). Patients received FCM...
doses of 15 mg/kg, with a maximum dose of 750 mg. Patients weighing 50 kg or more received two doses one week apart, while those weighing less than 50 kg received either one or two doses, based on the decision of their hematologist. All doses were infused over 15 minutes, and vital signs were monitored throughout the infusion and for 30 minutes following completion.

The median hemoglobin rose from 9.1 g/dL at baseline to 12.3 g/dL at the 4-12 week follow-up visit. Thirty-six patients (68%) had resolution of their anemia, with hemoglobin levels at or greater than normal for age, serum ferritin levels $\geq$ 15 ng/mL and/or total iron-binding capacity $\geq$ 425 mcg/dL. Another 30% of patients met the criteria for a partial response, defined as a rise in hemoglobin $\geq$ 1 g/dL above baseline. Only one patient failed to respond. Seven patients (16%) experienced an adverse effect. Five had evidence of a mild hypersensitivity reaction; four had urticaria and/or pruritus and one developed dyspnea during the infusion. All of these patients responded to diphenhydramine given alone or in combination with hydrocortisone. Only one of these patients was given a second dose, which produced similar symptoms. The two remaining adverse effects were tingling at the infusion site and an extravasation which produced staining at the infusion site. All of these events resolved without sequelae.

Similar findings were reported by Mantadakis and Roganovic in a letter to the Editor of The Journal of Pediatrics following publication of the previous study. The authors describe the results of FCM administration in 15 children and adolescents (ages 8-18 years, median age 12 years). The indication for treatment included anemia associated with heavy menstrual bleeding, gastrointestinal diseases, or nutritional iron deficiency. A total of 27 FCM doses were administered, all 500 mg except for one dose of 1,000 mg. Doses were diluted to a concentration $\geq$ 2 mg/mL in normal saline and administered over 30 minutes to 2 hours. The median pretreatment hemoglobin level of 7.3 g/dL (range 5.0-11.2 g/dL) rose to 12.6 g/dL (8.0-14.8 g/dL) at follow-up at least 4 weeks after treatment. Only one adverse effect was reported, an extravasation resulting in mild iron staining of the forearm.

**Warnings and Precautions**

Although FCM does not carry the black box warning shared by the other injectable iron products, it should not be used in patients known to have hypersensitivity to any of its components. Severe hypersensitivity reactions, including anaphylaxis, have been reported after FCM use. Investigations into the mechanism of hypersensitivity reactions to IV iron products have revealed both immunologic and non-immunologic mediated responses. It has been suggested that most cases are the result of mast cell activation, similar to the red man syndrome seen with vancomycin. This would support the finding that slowing subsequent infusions reduces the likelihood of a reaction.

Patients should be monitored for a minimum of 30 minutes following a dose of FCM, or until clinically stable. Administration should be done in a location with appropriate personnel and equipment for the management of anaphylaxis or other serious adverse reactions. Less severe hypersensitivity reactions, including rash, urticaria, pruritus, wheezing, and hypotension, have been reported in 1.5% of adult patients.

**Adverse Effects**

Transient hypertension has been reported in 3.8% of adults receiving FCM during clinical trials. Facial flushing, dizziness, nausea, or vomiting is reported in 2-7% of patients, typically occurring immediately after administration of a dose and resolving within 30 minutes. These adverse effects have not been observed in the pediatric studies, while mild hypersensitivity reactions have been more common. Extravasation with resulting discoloration of the skin around the injection site has been documented in 1.4% of adults in clinical trials, which is consistent with its frequency in the pediatric reports.

Hypophosphatemia is a known adverse effect of the parenteral products containing an iron-carbohydrate complex. Three recent papers suggest the risk is higher in patients receiving FCM than other forms of parenteral iron. In a retrospective study of 81 patients by Schaefer and colleagues at the Medical University of Innsbruck, the prevalence of hypophosphatemia ranged from 11-32%. The median time to development of hypophosphatemia was 41 days, with 13 patients exhibiting prolonged hypophosphatemia lasting more than 2 months. The risk of developing hypophosphatemia was independently predicted by baseline phosphate level and choice of iron preparation. The odds after FCM administration was 45.5%, compared to only 4% after administration of iron isomaltoside, a preparation not currently available in the United States.

The decrease in plasma phosphate levels following parenteral iron administration is believed to be mediated through an increase in intact fibroblast-growth factor 23 (iFGF-23), which results in reduced tubular resorption of phosphate. The mechanism by which FCM or other iron-carbohydrate complexes produce this effect is unknown. In most patients, hypophosphatemia is transient and produces no significant clinical symptoms. Some patients,
however, will develop prolonged or severe hypophosphatemia, with osteomalacia and fractures. Phosphate supplementation, with vitamin D supplementation and calcitriol, is recommended to prevent or correct deficiencies in patients receiving high-dose therapy or repeated courses of IV iron.\textsuperscript{11,13} An anti-iFGF23 antibody is currently under investigation that could potentially prevent this adverse effect in the future.\textsuperscript{11,12}

Dosing Recommendations
As with other parenteral iron products, doses of FCM are expressed in mg of elemental iron. The recommended FCM regimen for adults weighing 50 kg or more consists of two IV doses of 750 mg separated by at least 7 days, with a maximum dose of 1,500 mg per course. For adults weighing less than 50 kg, the recommended regimen is 15 mg/kg given at least 7 days apart. Treatment with FCM may be repeated as needed for recurrent iron deficiency anemia after a minimum of 7 days. Excessive doses of parenteral iron may lead to accumulation and hemosiderosis.\textsuperscript{3}

Ferric carboxymaltose may be given as an undiluted solution by slow IV push at a rate no more than 2 mL (100 mg) per minute. It may also be diluted in 0.9% sodium chloride to a concentration of 2 to 4 mg/mL and infused over at least 15 minutes. Pediatric studies and case series published to date have infused the drug over 30 minutes to 2 hours. Once diluted, FCM is stable at room temperature for 72 hours. The solution contains no preservatives, and any unused drug should be discarded.\textsuperscript{3}

Availability and Cost
Ferric carboxymaltose injection (Injectafer\textsuperscript{®}) is available in a 750 mg/15 mL (50 mg/mL) single use vial. The average wholesale price (AWP) is $935.75 per vial, making the cost of the recommended two dose regimen $1,871.50. In comparison, the AWP for a comparable regimen of ferumoxytol (Feraheme\textsuperscript{®}), two 510 mg doses, is approximately $1,500. The AWP for 1,000 mg of iron sucrose (Venofer\textsuperscript{®}), given in multiple doses, would be approximately $500. While the acquisition cost is considerably higher for the two newer products, the need for additional clinic visits may lessen the cost benefit of iron sucrose.

Summary
Recent clinical trials have shown the safety and efficacy of FCM in infants, children, and adolescents with clinically significant iron deficiency anemia. In patients who fail oral iron therapy, this product may be a safer method of treatment than other intravenous iron products on the market in the United States. The primary disadvantage of FCM is the greater risk for hypophosphatemia, requiring closer monitoring and possibly supplementation. Additional experience is needed to further define the incidence of this adverse effect and an optimal plan for its prevention or treatment.

References