

Clinical update: intravenous iron for anaemia

For nearly half a century, parenteral iron has been considered dangerous and for use only in extreme situations and when oral iron was not tolerated. This proscription was based largely on poorly characterised and infrequent anaphylactoid reactions to the high-molecular-weight dextran preparation (Imferon) that for most of this time was the only product available. Moreover, when parenteral iron was necessary, the recommended approach was small intramuscular doses (≤ 100 mg), even after intravenous administration of the total iron deficit as a single dose or as repetitive boluses was shown to be as safe and effective as the intramuscular route.¹⁻⁴ This mindset persists despite the subsequent introduction of low-molecular-weight iron dextran and two iron salt preparations, ferric gluconate and iron saccharate (the latter is also known as iron sucrose), all of which are associated with fewer serious adverse events than the high-molecular-weight dextran. The introduction of recombinant erythropoietin for dialysis patients was associated with the development, in some individuals, of functional iron deficiency that limited efficacy. Intravenous iron, unlike oral iron, improves erythropoietic response in dialysis patients,^{5,6} and is now routinely used.⁷

The discovery of the iron regulatory peptide, hepcidin, has improved our understanding of the anaemia of chronic inflammatory states, including cancer.^{8,9} Hepcidin is upregulated in these conditions, resulting in increased synthesis by the liver. Hepcidin inhibits iron transport across cell membranes, which decreases the accessibility of storage iron and gastrointestinal absorption of dietary

iron, leading to an increased frequency of iron-restricted erythropoiesis, especially during therapy with recombinant erythropoietin. The most frequent laboratory findings during the anaemia of chronic inflammation are hypoferraemia and a low percent transferrin saturation, although these findings are not always present. The increasing use of recombinant erythropoietin to treat anaemia in patients with chronic diseases has expanded the population of patients with functional iron deficiency and increased interest in safe rational approaches to parenteral iron therapy. There is mounting evidence that anaemic patients with cancer undergoing chemotherapy and receiving recombinant erythropoietin respond better when parenteral iron is administered.¹⁰⁻¹² This benefit is independent of baseline iron variables, such as ferritin, low percentage transferrin saturation,¹⁰ and stainable marrow haemosiderin,¹² leaving the clinician in need of laboratory variables to reliably detect iron-restricted erythropoiesis in patients with inflammatory illnesses and to predict improvement of erythropoietic response to parenteral iron in the setting of inflammatory illness. Two new laboratory measures look promising: percent hypochromic red blood cells and reticulocyte haemoglobin content.^{13,14} These tests are reliable and accurate correlates of functional iron deficiency. Although these investigations are not yet widely available, their use will probably expand and guide identification of functional iron deficiency and rational intervention with parenteral iron.

Currently, four parenteral iron preparations are available (table). No randomised trials have compared the safety and efficacy of any of these agents. The largest retrospective review of dialysis experience suggests that most serious adverse events have been associated with the high-molecular-weight iron dextrans (Imferon, which is no longer available and the current preparation, Dexferrum) and are rare ($<1:200\,000$) with the low-molecular-weight iron dextran or the two iron salts (figure).^{15,16} Adverse event rates might be somewhat higher in patients with inflammatory diseases in which immune-mediated drug reactions may be observed more commonly than in dialysis patients. Some of the adverse clinical experience with parenteral iron is due to inappropriate supportive care. Myalgias, when they include chest and back discomfort, are mistakenly described as anaphylaxis, prompting

	Low-molecular-weight iron dextran	Iron saccharate	Ferric gluconate	High-molecular-weight iron dextran
Test dose required	Yes	No	No	Yes
Vial volume	2 mL	5 mL	5 mL	1-2 mL
Iron per vial	50 mg/mL	20 mg/mL	12.5 mg/mL	50 mg/mL
Black-box warning	Yes	No	No	Yes
Total-dose infusion	Yes	No	No	Yes
Premedication	TDI only	No	No	TDI only
Preservative	None	None	Benzyl alcohol	None
Molecular weight measured by manufacturer	165 000 Da	34-60 000 Da	289-440 000 Da	265 000 Da

TDI=total-dose infusion.

Table: Currently available intravenous iron preparations

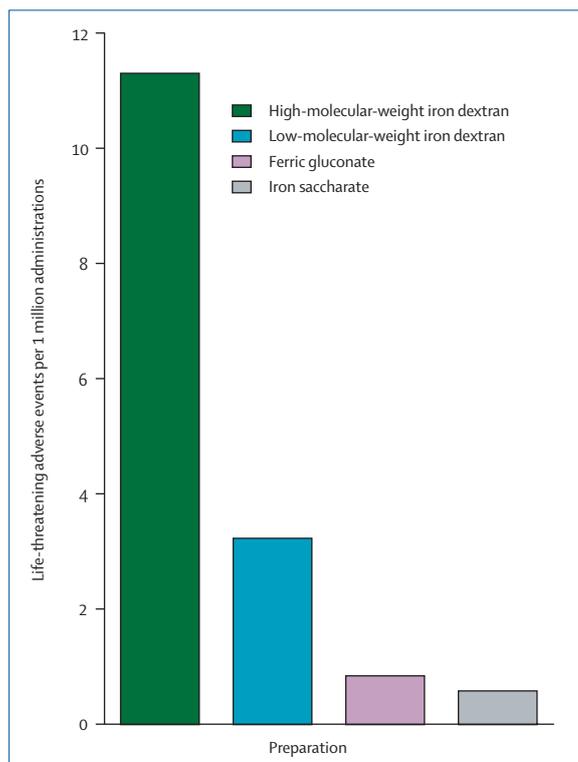


Figure: Relative rates of reported serious adverse events with the four different parenteral iron preparations¹⁶

From FDA Medwatch reports 2001–03, Chertow et al^{15,16} reported that high-molecular-weight iron dextran was associated with 3.2-fold increase in odds of adverse drug event and 3.4-fold increase in odds of life-threatening event.

unnecessary interventions with antihistamines and pressors and misleading clinicians about the toxicity profile of intravenous iron. The use of antihistamines as premedication can cause vasoactive reactions that are misinterpreted as a reaction to the injected iron. Antihistamines should not be given before intravenous iron administration.³

The clinical setting in which intravenous iron is used should be considered in the choice of iron preparation. For patients with uncomplicated iron deficiency, a single infusion of the total dose of low-molecular-weight iron dextran is the most convenient and cost effective.⁴ The replacement dose is calculated, diluted in normal saline and infused over 4 h.³ The dose, in mg iron, is calculated by: $(0.136 \text{ mg/kg times weight in kg}) \text{ times } ([\text{haemoglobin in g/dL times } 100 \text{ divided by } 14.8] \text{ minus } 100)$. An intravenous test dose of 25 mg of the diluted solution is required. If no adverse events occur within 1 h, the remaining solution can be administered. The administration of methylprednisolone before the test and after the infusion decreases the

incidence of myalgias and arthralgias.¹⁷ This total-dose infusion is most appropriate for iron deficiency due to pregnancy, menometrorrhagia, surgical blood loss, and gastric bypass and in those with uncomplicated iron deficiency who are non-compliant with or intolerant of oral iron. This approach is useful, for example, in patients with hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu disease) in which gastrointestinal losses exceed the ability of the small intestine to absorb oral iron. Intravenous iron is also appropriate for those patients with iron malabsorption, such as in coeliac disease, and for those with inflammatory bowel disease and iron deficiency. For total-dose infusion, dextran is the appropriate iron preparation, because the iron salts cause dose-dependent gastrointestinal or vasoactive reactions at doses above 200–400 mg.¹⁸ The preferred dextran is the low-molecular-weight preparation (InFed, North and South America; CosmoFer, Europe and Asia). For patients receiving cyclical therapies (cancer chemotherapy, haemodialysis), who are seen regularly by a physician, the iron salts or low-molecular-weight iron dextran can be used as short 100–400 mg infusions. One convenient approach is to administer 200 mg iron saccharate¹⁹ or 100 mg iron dextran²⁰ as a 2-min intravenous bolus. A test dose is not required with the iron salts, making their use in this setting particularly attractive. Although a test dose is still recommended with low-molecular-weight iron dextran, the value of this test has never been established. In our experience with more than 20 000 doses of low-molecular-weight iron dextran, no serious adverse events have been observed and the test dose has not altered the therapeutic plan.

Nonetheless, serious adverse events remain a concern. Acute myalgias (chest and back tightness) after a test dose without tachycardia, hypotension, wheezing, stridor, or periorbital oedema occur infrequently. This reaction abates within minutes without treatment and does not recur with rechallenge (Fishbane S, Winthrop University Hospital, New York, NY, USA, personal communication). This event should not be treated with diphenhydramine or epinephrine. When the total dose administered is less than 200 mg ferric gluconate or 400 mg iron saccharate, acute reactions are very uncommon. Adverse events with iron dextran are not related to the dose or infusion rate.³

What is the rationale for using intravenous iron? Oral iron is not without side-effects: gastrointestinal symptoms are so frequent that they cause serious

problems with compliance. Moreover, only a small amount of iron can be absorbed orally each day, even in patients without hepcidin-induced absorption difficulties. For patients whose daily iron loss exceeds their ability to absorb oral iron, parenteral iron is the only effective approach. For patients with cancer or other inflammatory conditions, an additional advantage to intravenous iron is that it overcomes the block to absorption and recycling of iron induced by hepcidin. Two randomised trials have compared the efficacy of oral and intravenous iron in anaemic patients with cancer receiving recombinant erythropoietin. In both studies, oral iron with recombinant erythropoietin was not significantly better than recombinant erythropoietin alone, but intravenous iron with recombinant erythropoietin resulted in a significantly better erythropoietic response,^{10,11} similar to the published results from patients on dialysis. Intramuscular iron has been an alternative to intravenous iron replacement because of misinformation that it was safer and less toxic. This treatment is painful, associated with gluteal sarcomas, causes permanent discolouration of the skin, and has never been shown to be less toxic than intravenous iron; therefore, it should be abandoned.

Because the safety and efficacy of the two different methods of intravenous iron administration are the same, the practitioner should determine whether repeated boluses or total-dose infusion best meets the needs of the patient's schedule. If boluses are used, doses should not exceed 400 mg per visit and are best given diluted in normal saline as a 30-min infusion without premedication or, if lower doses are used, as a 2-min intravenous push.^{19,20} Doses for total-dose infusion should be diluted in 500 mL normal saline, infused over 3–4 h after a test dose of the diluted solution, preceded and followed by 125 mg intravenous methylprednisolone.

The role of intravenous iron in clinical medicine is poorly understood and is an underused tool in the treatment of iron deficiency and anaemia in chronic disease states. This underuse is at least in part due to misinformation and misinterpretation of the incidence and clinical nature of serious adverse events. When high-molecular-weight iron dextran is excluded, there is no substantially increased risk with the administration of intravenous iron.

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