Safety of intravenous iron formulations: facts and folklore

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Introduction

It is unlikely that anyone reading this review was not taught that intravenous (IV) iron is dangerous. While early preparations were associated with an unacceptably high rate of serious adverse events, most notably anaphylactic shock, newer formulations with carbohydrate shells which bind the elemental iron more tightly, allowing for a much slower release, are very much safer with serious toxicity being marginal to absent in prospective trials. The perception of risk is fueled by misinterpretation and misinformation of the clinical nature of minor infusion reactions[1], inappropriate use of premedication with diphenhydramine[2] and inferences made about the relative safety of the available formulations using spontaneous adverse event reporting systems, methodologies proscribed by regulatory agencies[3,4]. In this article we review published evidence on the relative safety of the different formulations, highlight errors in interpretation and intervention when minor infusion reactions occur, and posit a paradigm for maximising safety with this underutilised therapeutic tool.

History of intravenous iron use

The first parenteral iron infusions were associated with severe acute reactions and unsuitable for use. With the development of iron dextran in 1954[5], IV iron could be given more easily, but severe acute reactions still occurred infrequently. In 1964, the first report of 37 patients receiving a total dose infusion (single replacement dose) was published in Blood[6], with one delayed reaction consisting of fever and chills without hypotension or wheezing. It was, however, another 16 years before the findings of the first prospective study in 471 patients were published in JAMA[7]. While all patients responded and none died, three developed signs of anaphylaxis, leading the authors to conclude that IV iron should be reserved for those clinical situations in which oral iron could not be used. Considering the inexpensive and readily available option of oral iron, it is not surprising that practitioners had little enthusiasm for IV iron, a treatment modality associated with shock, and subsequently ignored the nearly ubiquitous gastrointestinal perturbation and poor adherence associated with the use of oral formulations.

Then, in 1989, erythropoiesis-stimulating agents became available for use in dialysis patients, establishing a real need for IV iron. Imferon®, a high molecular weight (HMW) iron dextran which is no longer available, was the predominant product used. In 1991, Imferon® was removed from the market, but at the same time, INFeD®, a low molecular weight (LMW) iron dextran, was introduced. This was followed by the introduction of other iron dextrans, such as Dexferrum® (another HMW iron dextran) which was released for clinical use in the USA only, whereas INFeD®, which was branded as Cosmofer®, was also licensed in Europe. In 1999 and 2000, two iron compounds, ferric gluconate (Ferrlecit®) and iron sucrose (Venofer®), already in use in Europe, were approved for use in the USA. The smaller carbohydrate cores limit the dose of these agents to no more than 125 mg for ferric gluconate and 200-400 mg for iron sucrose. While 1,000 mg of LMW INFeD® can be administered safely in 1 hour[8], three new products which promise to allow safe, single-setting iron replacement dosing in 15 minutes, have been approved for clinical use. Two of these (ferumoxytol; Feraheme® in the USA and Rienso® in Europe; and ferric carboxymaltose (Injectafer® in the USA and Ferinject® in Europe) are available in both the USA and Europe, and one, iron isomaltoside-1000 (Monofer®) is available in Europe only (Table I).

Safety issues with intravenous iron

By 1990, the use of IV iron in dialysis centres had escalated rapidly. Imferon® was the formulation most used. Although serious adverse events occurred infrequently, the nephrology community rapidly adopted the addition of IV iron to the treatment paradigm of dialysis-associated anaemia with observed improvements in haematological and haematopoietic responses, levels of energy, activity, quality of life, cognition, work, sexual function and even decrements in doses of erythropoiesis-stimulating agents to achieve similar responses. However, in 1991, a contaminated lot of Imferon® resulted in the recall of the product worldwide. Serendipitously, at virtually the same time, INFeD®, a LMW iron dextran was approved for use and rapidly replaced the recalled HMW iron dextran. For 5 years, based on the overwhelming preponderance of published evidence, and with the anecdotal experience

Table I - Intravenous iron preparations.

	Currently available intravenous iron preparations					
Trade name	**INFeD®[1]**	**Ferrlecit®[2]**	**Venofer®[3]**	**Feraheme®[4]**	**Monofer®[5]**	**Injectafer®[6]**
Manufacturer	Watson Pharmaceuticals Inc.	Sanofi Aventis Inc.	American Regent Inc.	AMAG Pharmaceuticals	Pharmacosmos A/S	American Regent Inc.
Carbohydrate	Dextran Polysaccharides	Gluconate	Sucrose	Polyglucose sorbitol carboxymethylether	Isomaltoside	Carboxymaltose
Molecular weight measured by manufacturer (Da)	165,000 Low-molecular-weight iron dextran	289,000-444,000	34,000-60,000	750,000	150,000	150,000
Max. approved dosage (mg)	100	125	200	510	20 mg/kg	1,000 mg if patient weighs >66 kg
TDI possible	Yes	No	No	No	Yes	No
Premedication	TDI only	No	No	No	No	No
Test dose required	Yes	No	No	No	No	No
Iron concentration (mg/mL)	50	12.5	20	30	100	50
Vial volume (mL)	2	5	5	17	1, 5 and 10 in Europe	2 and 10 in Europe
Black box warning	Yes	No	No	No	N/A	N/A
Preservative	None	Benzyl alcohol	None	None	None	None

1 - INFeD® prescribing information, Watson Pharma, Inc. Morristown, NJ (USA): http://pi.actavis.com/data_stream.asp?product_group=1251&p=pi&language=E.
2 - Ferrlecit® Prescribing Information. Sanofi Aventis, Inc. Bridgewater, NJ (USA): http://products.sanofi-aventis.us/ferrlecit/ferrlecit.html.
3 - Venofer® prescribing information. American Regent, Inc. Shirley, NY (USA): http://www.venofer.com/PDF/Venofer_Insert_IN2340Rev_10-13.pdf.
4 - Feraheme® prescribing information. AMAG Pharmaceuticals, Inc. Waltham, MA (USA): http://www.feraheme.com/downloads/feraheme-pi.pdf.
5 - Monofer® prescribing information. Pharmacosmos UK Ltd. Thame, Oxfordshire, UK: http://www.monofer.com/media/60600/monofer_abbreviated_prescribing_information_04-2014.pdf.
6 - Injectafer® prescribing information. American Regent, Inc. Shirley, NY (USA): http://www.americanregent.com/documents/Product94PrescribingInformation.pdf.

N/A: not available; TDI: total-dose infusion. Injectafer® is marketed outside the USA under the brand name Ferinject®. INFeD® is marketed outside the USA under the brandname CosmoFer®.

of nephrologists during that time, the use of IV iron was associated with extremely few significant adverse events. Then, in February 1996, another HMW iron dextran (Dexferrum®) was approved as a less expensive alternative to INFeD®. Shortly thereafter, INFeD® was briefly unavailable for administrative reasons. Using Freedom of Information from the Food and Drug Administration, reported adverse events with IV iron increased 11-fold during that period[9]. In 1998, Case reported that virtually all serious adverse events with iron dextran were due to Dexferrum® and recommended its avoidance[10]. Similar conclusions were published by Mamula et al[11]. Nonetheless, large retrospective analyses, without differentiating between the two dextran formulations, concluded that serious adverse events were far less common with two other iron compounds, ferric gluconate and iron sucrose, and subjects with previous sensitivity to iron dextran were unlikely to react adversely to either of these two products[12-15]. As a result, virtually overnight, the entire dialysis population was switched from iron dextran to ferric gluconate or iron sucrose.

Then, in 2004, in a review of the USA Food and Drug Administration database of spontaneous adverse event reports, Chertow *et al.* found no significant differences in serious adverse events when ferric gluconate and iron sucrose were compared to LMW iron dextran[16]. The authors further concluded that when HMW iron dextran is avoided, intravenous iron is safe with an estimated serious adverse event incidence of <1:200,000[17]. While the Food and Drug Administration has specifically proscribed the use of this methodology to compare relative rates of adverse events among formulations[3], these conclusions are corroborated by the preponderance of published evidence[18] with only one publication extant reporting similar rates of adverse events between the two iron dextran formulations[19].

These conclusions are supported by several prospective head-to-head comparisons, intra-institutional retrospective studies and meta-analyses examining relative rates of adverse events among the available IV iron products. Two prospective studies with iron sucrose and LMW iron dextran found no difference[20,21]. A meta-analysis corroborated these findings[22]. In an intra-institutional retrospective analysis, Okam *et al.* reported similar findings with a higher incidence of minor adverse events being observed with iron sucrose[23]. Similar observations were made in trials comparing the newer formulations ferumoxytol and ferric carboxymaltose to iron sucrose[24,25]. There are no comparisons of the newer formulations with LMW iron dextran. Unfortunately, a recent study made the ill-considered decision to prospectively compare ferric carboxymaltose with the now unavailable HMW iron dextran, Dexferrum®, and concluded that fewer adverse events were observed with ferric carboxymaltose[26]. Until a head-to-head comparison is done with the recommended LMW iron dextran formulation, no conclusions can or should be drawn.

Management of minor infusion reactions

Two common interventions contribute to the perception of serious danger with the use of IV iron. All of the formulations can infrequently cause minor infusion reactions at the start of the infusion or test dose (still required with LMW iron dextan although there is no published evidence to support the recommendation). These reactions typically consist of either mild arthralgia/myalgia of the chest or flank or facial flushing[1,27]. All of these symptoms routinely abate without therapy, and plasma tryptase levels drawn after the reaction are always normal. While unproven, the symptoms are most likely due to minor reactions to labile plasma iron released with any of the formulations. Iron sucrose and ferric gluconate release the highest amounts of labile plasma iron after an injection, requiring much lower, more frequent dosing to administer the desired dose[28], LMW iron dextran next and the three newer agents, ferric carboxymaltose, ferumoxytol and iron isomaltoside-1000 the least[29]. Hypotension is extremely rare. Unnecessary intervention with pressors or antihistamines can turn these minor symptoms into haemodynamically significant serious adverse events. The second intervention is inappropriate use of diphenhydramine as hypersensitivity prophylaxis for IV iron. Diphenhydramine® can cause somnolence, diaphoresis, hypotension and tachycardia and in one prospective study of 285 patients receiving a 500 mg infusion of LMW iron dextran was responsible for the majority of perceived adverse events ostensibly attributed to the IV iron[2]. These data support the previous conclusion that it is misinterpretation and misinformation about the clinical nature and frequency of minor adverse events which fuel a still present folklore about the danger of IV iron.

Oxidative stress and infection

IV iron has been conjectured to have a number of other potential adverse consequences. These include exacerbation of oxidative stress and infections[30,31]. Generally, the human body has carefully conserved mechanisms to sequester iron safely so as to prevent oxidative injury, utilising proteins such as ferritin and transferrin. Because IV iron may overwhelm the ability of these proteins to bind iron, iron may become free in the circulation or present in excess in tissues, where iron's oxidative properties can be injurious. Poorly bound iron can react with hydrogen peroxide (Fenton reaction) resulting in the generation of hydroxyl radicals. Iron is converted back to its Fe^{2+} form by the Haber-Weiss reaction. In this process, continued substrate for ongoing iron-catalysed hydroxyl radical production and oxidative stress is perpetuated. Hydroxyl radicals are highly toxic, resulting in denaturing of lipids, proteins and DNA[31]. Intravenous iron preparations have been shown to induce oxidative stress and cytotoxicity in vitro, in animals, in normal human volunteers, and in dialysis patients. In tissue culture, IV iron causes oxidative stress and cellular damage in endothelial cells[32]. A single injection of iron dextran (500 mg/kg) to five of six nephrectomised rats resulted in oxidative stress in cardiovascular tissues for several weeks[33]. Similarly, dialysis patients experienced a rapid rise in plasma lipid peroxidation, and DNA and protein oxidation following the administration of IV iron[34,35]. In another study conducted in haemodialysis patients from Austria, IV iron sucrose administered during a dialysis session induced a rise in plasma total peroxide levels, but the magnitude of this increase was no greater than that in control patients randomised to receive no IV iron[36].

Although these studies do appear to support at least a transient increase in oxidative stress after IV iron injection in haemodialysis patients, the quality of the scientific data is questionable, with inadequate knowledge of the most meaningful method for measuring oxidative stress, along with a lack of clarity on what the results obtained in a laboratory setting mean for patients administered IV iron.

There are also no prospective data to support the contention that IV iron exacerbates infections, and several prospective and observational studies suggest the opposite[37,38]. Nevertheless inferential reports continue to link the use of IV iron and increased infection. Litton *et al.* using a meta-analysis, with no predefined endpoint in the pooled studies, or any dose-response association

with iron and infection risk, or any difference in mortality rates and other serious adverse events in the IV iron groups, recently concluded that while IV iron decreases transfusion rates, it increases infections[39]. In contradistinction, Hoen *et al.* prospectively evaluated 985 dialysis patients receiving IV iron as part of the treatment paradigm for dialysis-associated anaemia and found that central venous catheters, arteriovenous grafts, immunosuppression and a history of infection were associated with an increased infection rate, while the use of IV iron, total dose of IV iron and serum ferritin were not[37]. Further corroboration can be found in an analysis of 32,566 haemodialysis patients in whom no adverse effect on 2-year survival was observed with doses of iron of up to 1,000 mg over a 6-month period[38]. Supporting those conclusions, Brookhart *et al.* estimated the effects of various iron dosing patterns on risks of mortality and infection-related hospital admissions in 776,203 exposure/follow-up pairs[40]. Consistent with the data of Hoen *et al.*, while bolus dosing (linked to catheters) was associated with an increased risk of infection, maintenance dosing or dose of IV iron compared with no iron, was not. More recently, Munoz *et al.* reported on 2,547 peri-operative patients who underwent elective lower limb arthroplasty or hip fracture repair, with or without erythropoiesis-stimulating agents, and observed not only reduced transfusion rates and shorter time spent in hospital (p=0.0001), but no difference in infection rates[41]. Consistent with these data are the results of a randomised, controlled trial by Anker *et al.* in which patients with heart failure, including 40% with chronic kidney disease, who received IV iron, had improvements in quality of life and functional status without an increase in infections[42]. In brief, the current literature relating to IV iron administration and both oxidative stress and infection risk does not allow firm conclusions to be drawn.

Conclusions

Several recent prospective studies report the safety, ease, convenience and efficacy of complete or near-complete replacement doses of IV iron administered in a single setting (total dose infusion over 15-60 minutes)[8,43-45]. For subjects with disorders for which oral iron cannot overcome ongoing losses, such as heavy uterine bleeding, gastrointestinal bleeding, malabsorption syndromes and gastric bypass surgery, Osler-Weber-Rendu syndrome (hereditary haemorrhagic telangiectasia) and other causes of angiodysplasia, or associated with worsening of the underlying condition, as in inflammatory bowel disease, a total dose infusion is a more convenient and less expensive method of replacing iron. Compared to the side-effects present in the majority of people taking oral preparations, such as constipation, metallic taste, gastric cramping and thick green tenacious stool, the adverse events with IV iron are minor, infrequent and short-lasting. IV iron is consequently moving rapidly forward in the treatment paradigm. As published evidence supports a larger and earlier role for IV iron and raises the question of whether it should be frontline therapy in many conditions, it is more important than ever that inferences and conclusions on the relative safety of the available IV iron formulations be based on credible data. Based on all prospective and intra-institutional retrospective studies, when HMW iron dextran is avoided the remaining formulations are safe, and probably much safer than most physicians realise.

Keywords: intravenous iron, safety, iron deficiency.

Conflict of interests disclosure

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References

1) Auerbach M, Ballard H, Glaspy J. Clinical update: intravenous iron for anaemia. Lancet 2007; **369**: 481-3.
2) Barton J, Barton E, Bertoli L, et al. Intravenous iron dextran therapy in patients with iron deficiency and normal renal function who failed to respond to or did not tolerate oral iron supplementation. Am J Med 2000; **109**: 27-32.
3) Wysoski D, Swartz L, Borders-Hemphill V, et al. Use of parenteral iron products and serious anaphylactic-type reaction. Am J Hematol 2010; **86**: 650-4.
4) Auerbach M, Kane R. Caution in making references from FDA's adverse event reporting system. Am J Health System Pharmacy, 2012; **11**: 922-3.
5) Baird I, Podmore D. Intramuscular iron therapy in iron deficiency anaemia. Lancet 1954; **267**: 942-6.
6) Marchasin S, Wallerstein R. The treatment of iron-deficiency anemia with intravenous iron dextran. Blood 1964; **23**: 354-8.
7) Hamstra R, Block M, Schocket A. Intravenous iron dextran in clinical medicine. JAMA 1980; **243**: 1726-31.
8) Auerbach M, Pappadakis J, Bahrain H, et al. Safety and efficacy of rapidly administered (one hour) one gram of low molecular weight iron dextran (INFeD) for the treatment of iron deficient anemia. Am J Hematol 2011; **86**: 860-2.
9) Auerbach M, Coyne D, Ballard H. Intravenous iron: from anathema to standard of care. Am J Hematol 2008; **48**: 455-7.
10) Case G. Maintaining iron balance with total-dose infusion of intravenous iron dextran. ANNA J 1998; **25**: 65-8.
11) Mamula P, Piccoli D, Peck S, et al. Total dose intravenous infusion of iron dextran for iron-deficiency anemia in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2002; **34**: 286-90.
12) Faich G, Strobos J. Sodium ferric gluconate complex in sucrose: safer intravenous iron therapy than iron dextran. Am J Kidney Dis 1999; **33**: 464-70.
13) Michael B, Coyne D, Fishbane S, et al. Sodium ferric gluconate complex in hemodialysis patients: adverse reactions compared to placebo and iron dextran. Kidney Int 2002; **61**: 1830-9.
14) Coyne D, Adkinson N, Nissenson A, et al. Sodium ferric gluconate complex in hemodialysis patients. II. Adverse reactions in iron dextran-sensitive and dextran tolerant patients. Kidney Int 2003; **63**: 217-24.

15) Silverberg D, Iaina A, Peer G, et al. Intravenous iron supplementation for the treatment of the anemia of moderate to severe chronic renal failure patients not receiving dialysis. Am J Kidney Dis 1996; **27**: 234-8.
16) Chertow G, Mason P, Vaage-Nilsen O, et al. On the relative safety of parenteral iron formulations. Nephrol Dial Transplant 2004; **19**: 1571-5.
17) Chertow G, Mason P, Vaage-Nilsen, et al. Update on adverse drug events associated with parenteral iron. Nephrol Dial Transplant 2006; **21**: 378-82.
18) Rodgers G, Auerbach M, Cella D, et al. High molecular weight iron dextran: a wolf in sheep's clothing. J Am Soc Nephrol 2009; **19**: 933-4.
19) Walters B, Van Wyck D. Benchmarking iron dextran sensitivity: reactions requiring resuscitative medication in incident and prevalent patients. Nephrol Dial Transplant 2005; **7**: 1438-42.
20) Sav T, Tokgoz B, Sipahioglu M, et al. Is there a difference between the allergic potencies of the iron sucrose and low molecular weight iron dextran? Ren Fail 2007; **29**: 423-6.
21) Critchley J, Dunbar Y. Adverse events associated with intravenous iron infusion (low-molecular weight iron dextran and iron sucrose): a systematic review Transfus Alternat Transfus Med 2007; **9**: 8-36.
22) Moniem KA, Bhandari S. Tolerability and efficacy of parenteral iron therapy in hemodialysis patients, a comparison of preparations. Transfus Alternat Transfus Med 2007; **9**: 37-42.
23) Okam M, Mandell E, Hevelone N, et al. Comparative rates of adverse events with different formulations of intravenous iron. Am J Hematol 2012; **87**: E123.
24) Macdougall IC, Strauss WE, McLaughlin J, et al. A randomized comparison of ferumoxytol and iron sucrose for treating iron deficiency anemia in patients with CKD. Clin J Am Soc Nephrol 2014; **9**: 705-12.
25) Bisbe E, Garcia-Erce J, Diez-Lobo A, et al. A multicentre comparative study on the efficacy of intravenous ferric carboxymaltose and iron sucrose for correcting preoperative anaemia in patients undergoing major elective surgery. Br J Anaesth 2011; **107**: 477-8.
26) Hussain I, Bhoyroo J, Butcher A, et al. Direct comparison of the safety and efficacy of ferric carboxymaltose versus iron dextran in patients with iron deficiency anemia. Anemia 2013; **2013**: 169107.
27) Fishbane S, Ungureanu, Maesake J, et al. The safety of intravenous iron dextran in hemodialysis patients. Am J Kidney Dis 1996; **28**: 529-34.
28) Chandler G, Harchowal J, Macdougall I. Intravenous iron sucrose: establishing a safe dose. Am J Kidney Dis 2001; **38**: 988-91.
29) Jahn M, Andreasen H, Futterer S, et al. A comparative study of the physicochemical properties of iron isomaltoside 1000 (Monofer®), a new intravenous iron preparation and its clinical implications. Eur J Pharm Biopharm 2011; **78**: 480-91.
30) Fishbane S, Mathew A, Vaziri ND. Iron toxicity relevance for dialysis patients. Nephrol Dial Transplant 2014; **29**: 255-9.
31) Vaziri N. Understanding iron: promoting its safe use in patient with chronic kidney failure treated by hemodialysis. Am J Kidney Dis 2013; **61**: 992-1000.
32) Kamanna VS, Ganji SH, Shelkovnikov S, et al. Iron sucrose promotes endothelial injury and dysfunction and monocyte adhesion/infiltration. Am J Nephrol 2011; **35**: 114-9.
33) Lim CS, Vaziri ND. The effects of iron dextran on the oxidative stress in cardiovascular tissues of rats with chronic renal failure. Kidney Int 2004; **5**: 1802-9.
34) Salahudeen A, Oliver B, Bower J, et al. Increase in plasma esterified F2 isoprostanes following intravenous iron infusion in patients on hemodialysis. Kidney Int 2001; **60**: 1525-31.
35) Tovbin D, Mazor T, Vorobiov M, et al. Induction of protein oxidation by intravenous iron in hemodialysis patients: role of inflammation. Am J Kidney Dis 2002; **40**: 1005-12.
36) Scheiber-Mojdehkar B, Lutzky B, Schaufler R, et al. Non-transferrin-bound iron in the serum of hemodialysis patients who receive ferric saccharate: no correlation to peroxide generation. J Am Soc Nephrol 2004; **15**: 1648-55.
37) Hoen B, Paul-Dauphin A, Kessler M. Intravenous iron administration does not significantly increase the risk of bacteremia in chronic hemodialysis patients. Clin Nephrol 2002; **57**: 457-61.
38) Feldman H, Jaffe M, Robinson B, et al. Administration of parenteral iron and mortality among hemodialysis patients. J Am Soc Nephrol 2004; **15**: 1623-32.
39) Litton E, Xiao J, Ho KM. Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials. BMJ 2013; **347**: f4822.
40) Brookhart M, Freburger J, Ellis A, et al. Infection risk with bolus versus maintenance iron supplementation in hemodialysis patients. J Am Soc Nephrol 2013; **24**: 1151-8.
41) Munoz M, Gomez-Ramirez, Cuena J, et al. Very-short-term perioperative intravenous iron administration and postoperative outcome in major orthopedic surgery: a pooled analysis of observational data from 2547 patients. Transfusion 2014; **54**: 289-99.
42) Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 2009; **361**: 2436-48.
43) Auerbach M, Strauss W, Auerbach A, et al. Safety and efficacy of total dose infusion of 1020 mg of ferumoxytol administered in 15 minutes. Am J Hematol 2013; **88**: 944-7.
44) Qunibi W, Martinez C, Smith M, et al. A randomized controlled trial comparing intravenous ferric carboxymaltose with oral iron for treatment of iron deficiency of non-dialysis-dependent chronic kidney disease patients. Nephrol Dial Trans 2011; **26**: 1599-607.
45) Onken J, Bregman D, Harrington R, et al. A multicenter, randomized, active-controlled study to investigate the efficacy and safety of intravenous ferric carboxymaltose in patients with iron deficiency anemia. Transfusion 2014; **54**: 306-15.

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