Breaking New Ground in Intravenous Iron Therapy

a report by
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There is significant diversity in the availability of different parenteral iron preparations in Europe and the US. While non-dextran-containing iron formulations have been available in Europe for more than five decades, sodium ferric gluconate and iron sucrose have been available in the US only since the late 1990s and early 2000s, prior to which iron dextrans were the only available agents. Ferric carboxymaltose is now also approved for use in some European countries, but is not yet US Food and Drug Administration (FDA)-approved. Iron dextran use on both sides of the Atlantic has substantively declined with the advent of non-dextran irons, and iron sucrose has now attained over 50% of the European and US iron market.

Each of the iron preparations is effective in the management of iron-deficiency anaemia. However, there are substantial differences in physicochemical properties between the various complexes, resulting in variations in release characteristics of iron between formulations. Since such bioreactive iron may lead to oxidative stress reactions with cells and tissues, the result is that there are variations in the risk of the production of oxidative stress reactions from one iron formulation to another. In addition, dextran-containing parenteral iron preparations are associated with an elevated risk of allergic reactions, an effect that is much less common in non-dextran-containing preparations (see *Figure 1*). Therefore, not all iron preparations are equally safe.

Toxicities of Parenteral Iron Preparations

Comparisons of the rate and severity of toxicities of iron formulations are problematic. For example, one must consider whether there is any difference between an acute and a chronic iron load or overload, whether the method and rate of dosage delivery is important (e.g. does a schedule of 100mg intravenously [IV] three times per week for 10 doses impart the same toxicity potential as 500mg IV of the same iron preparation administered twice?) and is there any difference in the rate at which a given iron dose is administered (e.g. whether administered as a short bolus versus a prolonged infusion).[1] Many *in vitro* and *in vivo* studies have demonstrated a variety of adverse effects associated with iron, such as cytotoxicity, renal tubular damage, alteration of neutrophil function, promotion of atherosclerosis and free radical generation. Markers of oxidative stress have also been shown in humans, although they are predominantly limited to the haemodialysis population, since this is the most highly studied. Furthermore, observations suggested the association of markers of iron use (such as serum ferritin values) with poor outcomes, especially infection and mortality. Unfortunately, it is very difficult to extrapolate these findings to the real-life clinical use of parenteral iron for a number of reasons, including the use of different study designs, different inclusion and exclusion criteria, differing iron dosage regimens and the use of different markers of oxidative stress and outcomes.[1]

Toxicities of iron preparations may be classified into short- or long-term effects (see *Table 1*). Short-term effects include acute changes in some cellular or tissue functions following an oxidative stress insult, and allergic reactions. There is a strong correlation between the molecular mass of a complex and its robustness, which influences how rapidly bioactive iron can dissociate from the carbohydrate complex (see *Table 2*). Iron that is easily and rapidly released from a non-robust complex may overwhelm transferrin's ability to bind it. A large number of *in vitro* and *in vivo* studies have documented that this non-transferrin-bound iron can promote the formation of oxidative species, which can adversely influence cellular and tissue functioning.

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In general, dextran-containing and carboxymaltose complexes are the most robust, meaning that they have the lowest risk of such oxidative stress reactions. However, all iron products have been studied and all have been shown to promote oxidative stress to some degree. Many of these studies have been criticised for using concentrations of iron that are far in excess of those observed after typical doses that are used in routine clinical practice. The variability of study designs, iron doses, infusion rates, timing protocols and markers for oxidative stress exacerbate difficulties in rendering comparisons. Furthermore, the real clinical outcomes and importance of such phenomena are unclear, and it is possible that the acute effects measured in these studies are not easily extrapolated to potential long-term adverse effects, such as increases in cardiovascular mortality or risks of infection.

Hypersensitivity Reactions

Conversely, there is a real risk of hypersensitivity reactions with certain iron formulations and not with others. Allergic-type reactions are related

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to the dextran content of iron dextran preparations, not to the iron content, and therefore the non-dextran-containing preparations are largely spared the problems of hypersensitivity reactions.[2,3] Two retrospective studies examined serious adverse events reported to the FDA in the late 1990s and early 2000s. Both concluded that the risk of such a type 1 reaction is greatest for iron dextran preparations and is substantially less for gluconate and sucrose complexes. One study looked at the number of reported adverse events for a high-molecular-weight iron dextran (Dexferrum®), a low-molecular-weight dextran (Infed®), sodium ferric gluconate (Ferrlecit®) and iron sucrose (Venofer®).[2]

The authors obtained data on all adverse events in the US reported to the FDA between 2001 and 2003, and separated these into non-life-threatening and life-threatening (death, cardiac arrest, coma and anaphylactoid reaction). There were 1,141 adverse events reported per 30 million doses administered. The absolute rates of life-threatening adverse events were 0.6 per million for iron sucrose, 0.9 per million for sodium ferric gluconate, 3.3 per million for low-molecular-weight iron dextran and 11.3 per million for high-molecular-weight iron dextran. It was concluded that while the risk of adverse events is relatively low, the risk was lowest with the iron sucrose preparation and highest with iron dextrans.

Another study looked specifically at reports of allergic reactions to IV iron treatment with dextran (high- and low-molecular-weight combined), sucrose and gluconate complexes between 1997 and 2002.[3] A a result of the granularity of clinician reporting of these effects, the authors constructed four clinical categories describing hypersensitivity adverse events (anaphylaxis, anaphylactoid reaction, urticaria and angioedema), and converted their findings into 100mg dose equivalents. All-event reporting rates were 29.2, 10.5 and 4.2 reports per million 100mg dose equivalents, while all-fatal-event reporting rates were 1.4, 0.6 and 0.0 reports per million 100mg dose equivalents for dextran, sodium ferric gluconate and iron sucrose, respectively. Dextran had the highest reporting rates in all four clinical categories. Sodium ferric gluconate had intermediate reporting rates for urticaria and anaphylactoid reaction, and a zero reporting rate for the anaphylaxis clinical category. Iron sucrose had either the lowest or a zero reporting rate in all clinical categories (see *Figure 2*).[3]

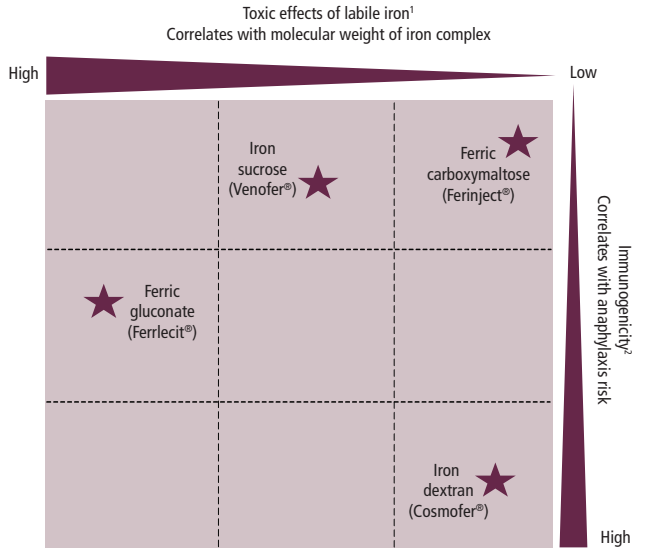
Ferric carboxymaltose, which is also non-dextran-containing, was not in use at the time of these studies. However, it is also likely to have a reduced risk of allergy. Therefore, the additional clinical benefits of non-dextran agents include the avoidance of test doses and pre-medication.

Mortality Associated with Parenteral Iron

For many years there has been ongoing controversy about the risk of long-term adverse effects, especially mortality. Two recent observational studies examined data from large US dialysis chains.[4,5] The sophisticated analysis, which sought to account for many co-morbid, confounding and time-dependent variables, concluded that long-term use of parenteral iron was not associated with increased risks of mortality. One of these examined data reported from over 32,000 haemodialysis patients within one dialysis chain in the US.[4] These patients had to have completed at least one year of dialysis between 1996 and 1997, when only iron dextran was available. For each month beginning six months after the end of the enrolment period and continuing until death or censoring, parenteral iron exposure over the most recent six months was categorised, with no iron received as the reference category. This rolling one-month risk of mortality associated with cumulative iron doses over the previous six months was determined over a 21-month period. Fitting multivariable models that appropriately account for time-varying measures of iron administration and many other fixed and time-varying measures of morbidity, the authors found no statistically significant association between any level of iron administration and mortality at doses up to 1,800mg over six months.

A second study reviewed records of 58,000 haemodialysis patients in the US, and included an examination of multiple markers of the malnutrition–inflammation–cachexia syndrome as well as those of iron status.[5] This study included patients being treated with non-dextran-containing iron preparations. Compared with those who did not receive IV iron, administered IV iron up to 400mg per month was associated with improved survival, whereas doses greater than 400mg per month tended to be associated with higher death rates. One additional interesting finding was that similar benefits accrued

Figure 1: Balance of Risks for Development of Oxidative Stress Reactions versus Hypersensitivity Reactions for Parenteral Iron Preparations



1. Van Wyck DB, J Am Soc Nephrol*, 2004;15:107–11.*
2. Hörl W, et al., Nephrol Dial Transplant*, 2007;22(Suppl. 3):iii2–iii6.*

Table 1: Classification of Toxicities Associated with Parenteral Iron

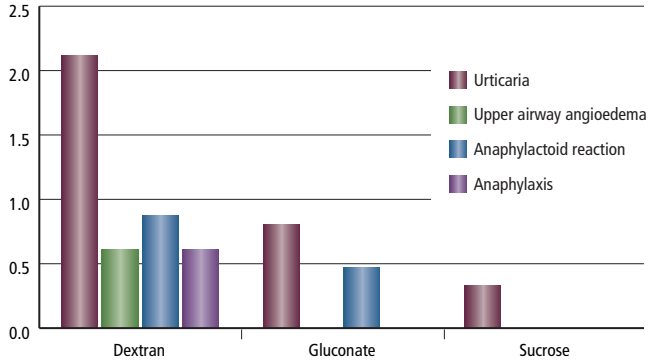
Short-term	Long-term
Dose-related (oxidative stress-related), allergic	Mortality infection

Table 2: Characteristics of Parenteral Iron Formulations

	Iron Dextran Ferric Carboxymaltose	Iron Sucrose	Iron Gluconate
Preparations	InFeD® Dexferrum® Ferinject®	Venofer® Fesin®	Ferrlecit®
Characteristic	Robust, strong	Semi-robust, moderately strong	Labile, weak
Molecular mass (kDa)	>100	30–100	<50
Degradation kinetics	Slow	Intermediate	Rapid
Potential for oxidative stress	Low	Moderate	High

Adapted from Crichton RR, Danielson BG, Geisser P (eds), In: Iron Therapy, with special emphasis on intravenous administration, 4th edition*, Uni-Med Verlag AG, 2008;71.*

Figure 2: Reporting Rates Per Million 100mg Dose Equivalents for Different Hypersensitivity Clinical Categories



from serum ferritin values of up to 1,200ng/ml, which is well in excess of published target ferritin ranges for most conditions.[5]

Ferric Carboxymaltose (Ferinject®)

Currently, there are fewer data available regarding ferric carboxymaltose (FC). This preparation is classified as a robust, non-dextran-containing complex with characteristics that result in the slow release of iron and a very low risk of hypersensitivity reactions (see *Table 2*). Interestingly, the low iron release rate enables this agent to be administered at doses of up to 1,000mg in short infusions over 15 minutes or up to 200mg as a push injection. Studies have been published that have been powered to examine efficacy as the primary end-point, with observations on safety as a secondary outcome. Preliminary findings suggest that it has a safe profile.

Furthermore, these studies have been conducted in patient populations with a wide variety of iron-deficiency anaemia disorders, rather than being limited to the anaemia associated with chronic kidney disease. For example, one study compared the efficacy and safety of IV FC (n=227) versus oral ferrous sulphate (n=117) in patients with post-partum iron-deficiency anaemia.[6] The FC was dosed at a maximum of 1,000mg iron over 15 minutes once per week (or 15mg/kg bodyweight [BW]) until the calculated total dose had been administered (maximum three infusions). Oral ferrous sulphate was dosed at 100mg twice per day for 12 weeks. The adverse effect profiles were very similar, with 26% of women experiencing adverse events with FC and 22% with ferrous sulphate. The breakdown of reported events was interesting and are reported here for FC and ferrous sulphate, respectively: nasopharyngitis (3.1 versus 1.7%), constipation (0.4 versus 6.8%), headache (2.6 versus 1.7%), elevation of C-reactive protein (1.8 versus 0%) and burning at the injection site (2.2 versus 0%).[6] Thus, mild adverse events from FC were offset by well-known gastrointestinal adverse events from oral iron.

In another study, FC (n=137) was compared with oral ferrous sulphate (n=63) in patients with iron-deficiency anaemia associated with inflammatory bowel disease.[7] FC was again administered up to a maximum of 1,000mg iron (or 15mg/kg BW) per infusion at one-week intervals until the patient's calculated total iron deficit was reached. Oral iron was given at 100mg twice a day for 12 weeks. The primary objective was to determine the non-inferiority of the efficacy of FC compared with oral iron. A secondary objective was to assess safety. FC was well tolerated. The reported adverse events for FC and oral iron, respectively, were: patients with more than one treatment-related adverse event (28.5 versus 22.2%), more than one serious adverse event (6.6 versus 0%), more than one adverse event leading to discontinuation from the study (1.5 versus 7.9%) and death (0.7 versus 0%). Death was not felt to be related to the use of FC. The most common adverse events for FC and oral iron, respectively, were: abdominal pain (2.9 versus 3.2%), nausea (2.2 versus 4.8%), headache (2.9 versus 1.6%) and diarrhoea (0.7 versus 6.3%).

Conclusion

The management of anaemia continues to quickly evolve as new information is published on the mechanisms and comparative incidences of toxicities of iron preparations and as experience with new iron preparations grows. It is clear that dextran-containing iron preparations have a high, and arguably unacceptable, risk of hypersensitivity reactions. On the other hand, iron dextrans are highly stable and carry a low proclivity for oxidative stress reactions. Iron sucrose has a very low incidence for type 1 reactions, and its huge worldwide experience indicates that it is a well tolerated and safe preparation. However, as it is a less robust complex than iron dextrans, it must be given in smaller doses. FC appears to have the combined advantages of being non-dextran-containing, and therefore not predisposed to high risks of anaphylactoid reactions, and being robust, hence being associated with a low risk of oxidative stress reactions. Furthermore, the ability to administer large doses of FC in short infusion times or as a push injection is a highly attractive characteristic, especially in clinic or outpatient settings, where it can avoid the need to delay patients and the need to have them return for repeated injections. ■

> Ferric carboxymaltose appears to have the combined advantages of being non-dextran-containing, and therefore not predisposed to high risks of anaphylactoid reactions, and being robust.

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