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Beyond efficacy and safety—the need for convenient and cost-effective iron therapy in health care

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Abstract

The National Service Framework advocates correction of anaemia in patients with chronic kidney disease (CKD). Oral iron is insufficient, while intravenous (IV) supplementation replenishes and maintains iron stores. Previously, effective delivery of iron therapy using available parenteral preparations has been hampered by dosing schedules and the need in some cases of a test dose. The introduction in Europe of newer iron preparations, including iron isomaltoside 1000 (Monofer) and iron carboxymaltose (Ferinject), now offers a potentially safe, effective and time-efficient method of outpatient iron repletion. This may potentially lead to better cost-effectiveness in a resource-limited service.

Keywords: anaemia; iron; cost; patient choice; kidney

Introduction

Chronic kidney disease (CKD) is a worldwide public health problem that affects approximately 6% of the UK adult population and is associated with a high prevalence of cardiovascular disease and large economic burden [1]. Anaemia occurs early during the course of CKD and progressively increases as a result of iron and erythropoietin deficiencies. The incidence of pre-dialysis anaemia in patients attending the renal service has been estimated to be around 68% of all patients referred for the first time for assessment with 61% having either absolute (depletion of both circulating and iron stores) or functional (depletion of circulating/available iron) iron deficiency [2,3].

The Renal National Service Framework and Best Practice Guidelines advocate correction of anaemia in patients with CKD not yet on renal replacement therapy [4,5]. Only 26% of these patients, however, receive replacement intravenous (IV) iron therapy.

The increasing use of erythropoiesis-stimulating agents (ESAs) has also led to a rapid increase in the need for adequate iron replacement therapy to maintain sufficient iron stores. This is essential for maximizing the effects of ESA therapy [6,7]. Recent randomized clinical studies have raised safety concerns of using ESA agents and their potential toxicity. Indeed, the risks of pure red cell aplasia (PRCA), thrombotic potential and possibly neoplasm make ESAs less attractive [8–10]. It is not clear from these recent publications whether the increased incidence of adverse cardiac and other events including stroke is due to the actual haemoglobin level achieved (i.e., a normal haemoglobin concentration of 13 g/dL or greater), the drug preparation itself (ESA), the dose of the drug used (i.e. high doses used in patients with possible ESA hyporesponsiveness) or an unrecognized factor which may be impacting on patients' morbidity and mortality. With these recent data concerning ESAs, correction of iron deficiency with IV iron may, perhaps, represent a safer option to optimize anaemia management in CKD patients. The NICE guidelines also suggest that iron replacement is required for CKD patients with low haemoglobin prior to ESA use [11]. By optimizing iron stores and iron bioavailability, ESA efficiency can be maximized, its requirement potentially delayed and patient quality of life improved [2,8,12].

What properties should the ideal iron preparation possess?

In considering the potential 'ideal' iron preparation, consideration must be given to the requirements of the clinician, health service and most importantly the patient in addition to the drug's pharmacological characteristics such as method of administration and flexibility of use.

Oral iron, although possibly more convenient, remains a poor substitute because of its poor bioavailability and compliance [13,14]. Iron delivery is restricted by inflammation which is commonly present in CKD. The mechanism is unclear but putatively involves hepcidin, a 25-amino acid synthesized in the liver. Hepcidin acts as a regulator of iron metabolism with effects on absorption, transportation and storage [15]. Hepcidin binds to the iron exporter channel ferroportin which causes internalization and degradation of iron [16]. This subsequently leads to reduced red cell iron

absorption and sequestration in the reticulo-endothelial system. To overcome this increased hepcidin synthesis and hence reduced iron absorption leading to anaemia, the most effective method is via the IV route of iron administration [6,7]. Used in isolation, IV iron leads to a significant rise in haemoglobin concentrations in the order of 0.6–2.7 g/dL [17,18].

Use of parenteral iron therapy for the treatment of anaemia dates back to 1932 when it was first administered by Heath *et al.* [19]. However, it was found to have significant 'disagreeable symptoms, sometimes severe and possibly dangerous' even with a modest dose of 40–80 mg [19]. Subsequently, in 1946, Goetsch *et al.* examined ferric hydroxide but found that it also caused numerous adverse problems [20]. Then, in 1947, Nissim discovered that use of an iron saccharide preparation appeared to be much safer [21]. Finally, Baird and Podmore in 1954 developed an iron dextran preparation (Imferon), which showed some initial promise but was withdrawn in 1992 due to a high incidence of anaphylactic reactions [22]. Since then, there has been resurgence in developing a useful and clinically practical parenteral iron therapy that would overcome the issues regarding safety associated with traditional iron therapies, related to anaphylaxis/immunogenicity and release of free or labile iron. Currently, several iron preparations have been in regular clinical use, but all possess various limitations to the 'ideal' situation. More recently, several next generation IV iron preparations have become commercially available. For the clinician, the decision about the qualities of the 'perfect' parenteral iron preparation remains to be confirmed, but the future potentially looks bright.

Delivery of iron

For an 'ideal' parenteral iron preparation, safety is critical and has been demonstrated in several studies for the current therapies [23–25]. In particular, there should be a low anaphylactic or anaphylactoid potential, and the preparation should not have a significant detrimental effect on renal function.

When IV iron is administrated, it passes to the reticulo-endothelial system (RES). The iron complex splits, and the iron is then combined to ferritin or transferrin which is used in haemoglobin production and storage. However, a small percentage of iron may be released as free iron. Hence, when considering the potential molecular structure of an ideal iron formulation, binding of the iron to the carbohydrate complex is critical to ensure that the complex allows tight binding of iron with minimal release of free iron that does not bind to transferrin. However, critical to iron's importance in biological processes is its ability to cycle reversibly between its ferrous and ferric oxidation states. This specific property, which is essential for its functions, also makes it hazardous because free iron can catalyze the formation of free radicals leading to cell damage. Labile iron (catalytic iron) consists of chemical forms that can participate in redox cycling. This property enables it to generate powerful oxidant species such as hydroxyl radical and/or reactive iron–oxygen complexes such as fer-

ryl or perferryl ion [26]. These complexes then propagate lipid peroxidation. In addition, iron can directly catalyze lipid peroxidation, the oxidative reaction of polyunsaturated lipids, by removing hydrogen atoms from polyunsaturated fatty acids in the lipid bilayers of organelle membranes [26]. Iron chelators may provide a protective effect, thus establishing a cause–effect relationship, at least in animal models.

In a population of CKD patients, debate remains regarding the effects of IV iron on renal function and proteinuria. Several animal models have demonstrated the potential detrimental effects of free iron on glomerular function [27]. This may be related to the putative toxic effect of iron to cells, in particular glomerular and mesangial cells via oxidative stress (lipid peroxidation) and cell cytotoxicity leading to endothelial dysfunction which leads to proteinuria, accelerated atherosclerosis and potentially an increase in serum creatinine. Previously, Zager *et al.* demonstrated *in vitro* in animal studies that the loosely bound parenteral iron formulations may cause direct cytopathic changes to renal cells (particularly mesangial cells and endothelial cells) and this, therefore, may potentially cause renal deterioration [27–29]. There are a few human studies, but Agarwal in a study of 20 CKD patients suggested that there was an increase in oxidative stress markers when IV sucrose was given, and this could, in part, be abrogated by *N*-acetyl cysteine [30]. However, this intervention did not affect proteinuria, a strong surrogate marker of renal progression leading to the possibility of direct 'drug-induced toxicity'. Recently, Shah *et al.* in preliminary studies carried out in India compared catalytic iron in subjects with either no renal disease or diabetes, with patients with diabetes and demonstrated that patients with overt diabetes have an increase in urinary catalytic iron which may be toxic to renal cells [31].

More recent clinical data on the neutral effects of IV iron on renal function are encouraging [32]. Indeed, 1-year data demonstrate this trend for low-molecular-weight iron dextran (Cosmofer) (Figure 1) [32]. Also, post hoc subanalysis of the FAIR-HF study in a population of NYHA class II/III heart failure patients with iron deficiency anaemia and a mean eGFR (MDRD) of 64 ± 21 mL/min/1.73 m^2 demonstrated a modest improvement in eGFR over a 24-week period after iron repletion in the order of 44 ± 1.7 mL/min in comparison to placebo [33]. Again, short-term data on iron isomaltoside 1000 (Monofer) are encouraging in relation to renal function [34]. These next generation preparations will be subjected to future ongoing scrutiny in longer-term studies.

The carbohydrate used in these next generation preparations mechanistically vary slightly but in essence assist in isolating the bioactive iron from plasma components until the iron–carbohydrate complexes enter the RES for subsequent entry into the intracellular storage iron pool (ferritin) or transfer to plasma transferrin for haemoglobin production. For iron carboxymaltose (Ferinject), the unique carboxymaltose shell leads to a highly stable, type I polynuclear iron (III)–hydroxide carbohydrate complex that completely surrounds the iron core with the release of minimal amounts of iron into the circulation, while for iron isomaltoside 1000, rather than surrounding the iron
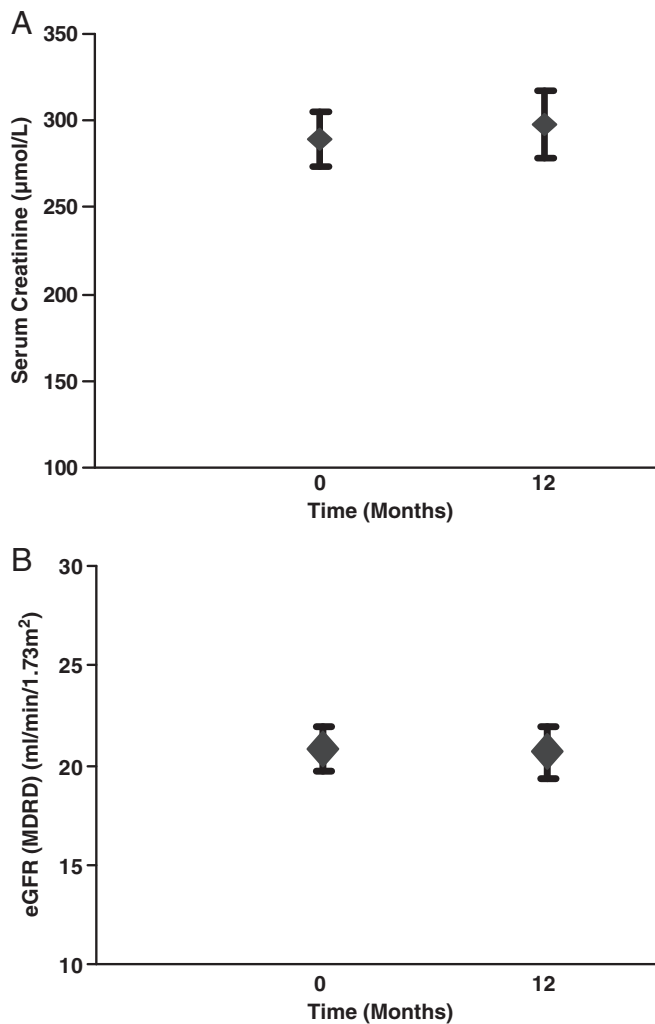
Fig. 1. **A**. Serum creatinine at baseline and after 1 year of intravenous iron therapy. Data are mean ± SEM. **B**. eGFR (MDRD) at baseline and after 1 year of intravenous iron therapy. Data are mean ± SEM.

core, the iron is enmeshed within the carbohydrate complex forming a matrix which may allow a more gradual release of iron. These novel mechanisms ensure that only minimal quantities of ionic iron are released from their carbohydrate shell/matrix which seem to ensure that free iron adverse effects and subsequent tissue toxicity from reactive oxygen species are negated.

Methods of administration of parenteral iron preparations

Flexibility of iron administration is important in all clinical situations. Iron has expanded its use beyond dialysis, pre-dialysis and in conservative CKD patients. It is currently a useful therapy in patients with anaemia and chronic transplant dysfunction [35]. Currently, a number of other speci-alities are utilizing IV iron but often seek assistance from their colleagues within the renal department for its admin-istration. These include cardiology (heart failure) [36], gastroenterology (inflammatory bowel disease) [37,38], haematology, oncology, gynaecology [39], post-partum an-aemia [40], and both pre- and post-operative use. In oncol-ogy, with the continued controversies of ESAs and carcinoma, use of iron represents an ideal solution as mild to moderate anaemia occurs in up to 75% of cancer pa-tients undergoing therapy [41]. Again, in inflammatory bowel disease, anaemia occurs in between 30% and 70% of patients. This may be due to a number of factors includ-ing chronic diarrhoea, vitamin B12 deficiency, folate defi-ciency and medication-induced bone marrow suppression, but the most common cause is iron deficiency from a com-bination of intestinal blood loss and reduced absorption from the gut as a result of hepcidin and chronic illness [42]. Indeed, there have been several studies of iron car-boxymaltose use in these populations [33,38,39,43,44], and in all cases, the introduction of parenteral iron has allowed a reduction of transfusions and thus reduced the inherent risks associated with blood transfusions such as infection, antibody development and transfusion resist-ance. Indeed, there is also a reduced risk of panel-reactive antibody development, critical in future transplantation success, which increases more than 2-fold with between one and five blood transfusions administered. Hence,

Table 1. Modes and dosage regimes of administration

Preparation	Methods of administration (dosing regime)		
	Repeated low dose and bolus administration	Intravenous drip Moderate dose infusion	Intravenous drip Total dose infusions
	(100–510 mg)	(200–1000 mg)	>1000 mg
Low-molecular-weight iron dextran (Cosmofer)	≤200 mg	≤1000 mg	1500 mg ~4–6 h (3 h[a]), Up to 20 mg iron/kg ~4–6 h + test dose
Iron sucrose (Venofer)	≤200 mg	≤200 mg	Not applicable
Iron gluconate (Ferelecit)	125 mg	Not applicable	Not applicable
Iron isomaltoside 1000 (Monofer)	≤200 mg	≤1000 mg not exceeding 20 mg iron/kg	1000–2000 mg ~1 h 0–10 mg iron/kg ~30 min 11–20 mg iron/kg ~60 min
Iron carboxymaltose (Ferinject)	≤200 mg	≤1000 mg not exceeding 15 mg iron/kg	Not applicable
Feraheme (ferumoxytol)	= 510 mg	510 mg	Not applicable

[a]Accelerated dose infusion regime used by the author and several other units [50].

reversion back to giving blood transfusions, unless absolutely clinically imperative, should be avoided in the future.

When examining the currently available iron preparations, several administration regimes are possible, including giving iron as a single total replacement dose, as repeat low doses or as a bolus. Previously, only low-molecular-weight iron dextran could be given as a total dose infusion of ≥1000 mg in a single episode, thus sparing veins and time and being more ideal for a non-captive population such as a CKD group. However, the three newer parenteral iron preparations appear to possess this property. For example, Feraheme (ferumoxytol), a semi-synthetic polysaccharide-coated iron oxide, can be administered over 17 s in doses

of up to 510 mg and repeated within a week [45–47]. Iron carboxymaltose allows administration as a single dose of up to 1000 mg (not exceeding 15 mg/body weight) in at least 15 min [43,44,48]. More recently, iron isomaltoside 1000 as a single dose of ≥1000 mg (not exceeding 20 mg/kg bodyweight) can be administered over 30–60 min [34,49]. Table 1 summarizes the modes and dosage regimes of administration.

The removal of the need for a test dose for iron administration is an essential prerequisite of an 'ideal' iron preparation to optimize efficiency of administration and cost. The ability for total dose infusion (TDI) replacement is also desirable. Currently, there appears to be no detrimen-

Table 2. The newer iron preparations in a clinician's wish list for the ideal iron preparation

Product	Low-molecular-weight iron dextran (Cosmofer)	Iron sucrose (Venofer)	Iron gluconate (Ferelecit)	Iron isomaltoside 1000 (Monofer)	Iron carboxymaltose (Ferinject)	Ferumoxytol (Feraheme)
Molecular weight, kDa	165	34–60	290–440	150	150	750[a]
pH	5.2–6.5	10.5–11.1	7.7–9.7	5.0–7.0	5.0–7.0	6.0–8.0
Carbohydrate	Dextran branched polysaccharide	Sucrose disaccharide	Gluconate monosaccharide	Isomatoside unbranched linear oligosaccharide	Carboxymaltose branched polysaccharide	Oxide coated with polyglucose, sorbitol, carboxymethylether
Maximum single dose	20 mg/kg	200 mg	125 mg	20 mg/kg	15 mg/kg single dose limit 1000 mg	510 mg
Maximum single dose administration 80 kg male	1600 mg	200 mg	125 mg	1600 mg	1000 mg	510 mg
Maximum single dose administration 60 kg female	1200 mg	200 mg	125 mg	1200 mg	900 mg	510 mg
TDI repletion	Yes	No	No	YES	No	No
Infusion within 1 h	No	NA	NA	Yes	Yes	Yes
Iron concentration, mg/mL	50	20	12.5	100	50	50
Test dose required	Yes	No/Yes (only Europe)	No	No	No	No
Minimally analytical free iron	<1%	10%	10–20%	<0.1%	<1%	<0.1%
Dose adjustment on dialysis	None	None	None	None	None	None

[a]Molecular weight for ferumoxytol is not comparable to the other iron values because of measurement to a different standard

tal effect of TDI iron apart from those recognized in its side effect profile [26,32]. If we compare the properties of the iron preparations currently available in Europe and the UK, the newer iron preparations 'tick the boxes' in a clinician's wish list for the ideal iron preparation (Table 2).

Convenience and cost-effectiveness

On the clinician's 'wish list', the flexibility of the iron preparation is one important factor in the choice of iron preparation, while other factors potentially influencing choice relate to convenience to patients and staff. We have previously shown that these have significant influences on choice in addition to cost [32]. An important factor is time. Patients have found that the time saved for them as a result of more effective and efficient delivery of iron therapy has led, for them, to benefits including less disruption to their personal life, less time away from both their home environment and work, less time away from their family and friends, and a reduced amount of time spent travelling for therapy as a result of more local administration of treatment and less treatment episodes [32]. These factors have all had a beneficial financial impact on patients and potentially to the wider community with less absence from work. Development of local services where the newer preparations can be administered may enhance this further. The ability to administer flexibly a total repletion dose of parenteral iron and the future costs of the parent drug may determine future prescribing practices as the other added clinical beneficial properties or parenteral iron between iron preparations become nullified.

For patients suffering from CKD or any other pathology linked to iron deficiency, quality of life is critical and can be objectively improved with parenteral iron therapy [41]. Indeed, iron therapy has reduced the risk to patients as a result of fewer blood transfusions, which carry their inherent risk of transmission of infection and Creutzfeldt–Jakob disease, fewer side effects and importantly for those with progressive renal disease preservation of veins for future vascular access.

The health service and staff also reap potential benefits from the newer iron therapies. More efficient use of the health service with a reduced treatment waiting time and total number of visits (from less frequent iron administration) all lead to savings in both nursing and medical time. It will allow an increased capacity to give treatment and have significant economic benefits which will allow more patients to receive treatment with a finite and often limited budget. This potential cost-effectiveness has already been demonstrated in several studies of IV iron use [32,47]. There is a growing wealth of clinical data to reassure, but this remains the most critical element for the future use of newer iron preparations.

Conclusion

Clinical practice is normally not based on cost alone but includes medical and patient considerations. The clinical evaluation of the efficacy (IV iron can work) and effective-ness (IV iron does work) without any detriment to quality of life or increase in side effects is important, but maximizing convenience and cost-effectiveness are equally important. This ethos is in line with the views on 'patient choice' and more importantly the concept of providing a service for patients without compromising on quality of care given. Therefore, in this new era of patient-directed therapy, the profile of the 'ideal' iron preparation should be capable of delivering sufficient quantities of IV iron to correct iron deficiency rapidly, with minimal potential side effects including low catalytic/labile iron release and negligible immunogenicity (risk of anaphylaxis). For preservation of veins, the IV preparations should have a neutral pH and have a wide dosing range to allow a single repletion dose, with no requirement for a test dose. Finally, it should be convenient and cost-effective for the patient, doctor and staff with maximal time efficiency.

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