Use of Intravenous Iron Supplementation in Chronic Kidney Disease
An Update

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Iron deficiency is an important clinical concern in chronic kidney disease (CKD), giving rise to iron-deficiency anemia and impaired cellular function. Oral supplementation, in particular with ferrous salts, is associated with a high rate of gastrointestinal side effects and is poorly absorbed, a problem that is avoided with intravenous iron. The most stable intravenous iron complexes (eg, iron dextran, ferric carboxymaltose, ferumoxytol, and iron isomaltoside 1000) can be given in higher single doses and more rapidly than less stable preparations (eg, sodium ferric gluconate). Iron complexes that contain dextran or dextran-derived ligands can cause dextran-induced anaphylactic reactions, which cannot occur with dextran-free preparations such as ferric carboxymaltose and iron sucrose. Test doses are advisable for conventional dextran-containing compounds. Iron supplementation is recommended for all CKD patients with anemia who receive erythropoiesis-stimulating agents, whether or not they require dialysis. Intravenous iron is the preferred route of administration in hemodialysis patients, with randomized trials showing a significantly greater increase in hemoglobin levels for intravenous versus oral iron and a low rate of treatment-related adverse events. In the nondialysis CKD population, the erythropoietic response is also significantly higher using intravenous versus oral iron, and tolerability is at least as good. Moreover, in some nondialysis patients intravenous iron supplementation can avoid, or at least delay, the need for erythropoiesis-stimulating agents. In conclusion, we now have the ability to achieve iron replenishment rapidly and conveniently in dialysis-dependent and nondialysis-dependent CKD patients without compromising safety.

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Review

IRON DEFICIENCY IN KIDNEY DISEASE

Iron deficiency is an important clinical concern in chronic kidney disease (CKD), arising from multiple factors directly or indirectly related to kidney dysfunction.[1-3] Dietary intake of iron may be inadequate due to poor appetite or advice to consume a low-protein diet, possibly exacerbated by chronic iron loss from repeated intestinal bleeding resulting from CKD-related abnormal platelet function. The chronic inflammatory status of many CKD patients induces increased hepcidin synthesis, which in turn inhibits uptake of dietary iron by enterocytes and export of iron from enterocytes, macrophages, and storage cells. These effects restrict the availability of iron for hemoglobin synthesis and other functions. In patients undergoing hemodialysis, regular blood loss compounds these problems, but even in nondialysis CKD (ND-CKD), iron deficiency

is estimated to affect over half of all adults with CKD Stage 3 or 4.[4] Iron deficiency is particularly prevalent in CKD patients receiving treatment with an erythropoiesis-stimulating agent (ESA) due to the marked increase in the demand for iron,[1] and is a major cause of nonresponsiveness to ESA therapy with associated negative implications for anemia correction and healthcare costs.[5]

In addition to the well-recognized consequences of iron-deficiency anemia, such as fatigue, reduced exercise capacity,[6] and potentially serious consequences for the patient's health and quality of life, iron deficiency also impairs other critical cellular functions such as the generation of cellular energy in skeletal and heart muscle, oxygen storage in myoglobin, T-lymphocyte proliferation and function, neuron myelination, and DNA synthesis. Recognizing the pivotal metabolic role of iron, the European Best Practice Guidelines[7] and the Kidney Disease Outcomes Quality Initiative[8] recommend a minimum serum ferritin level above 100 ng/mL and a minimum transferrin saturation (TSAT) greater than 20% in ESA-treated CKD patients. In addition, the recently published Kidney Disease Improving Global Outcomes Clinical Practice Guideline for Anemia in CKD recommends even more liberal thresholds for the use of iron therapy, suggesting that clinicians consider the potential for iron to increase hemoglobin in patients who have a serum ferritin concentration of 500 ng/mL or less and a TSAT level of 30% or less.[9]

METABOLISM OF IRON

Iron in the body is primarily found in the form of hemoglobin within erythrocytes (accounting for approximately 60% of all iron), within myoglobin in the muscles, and stored in the protein ferritin and, to some extent, in hemosiderin.[10] A small amount (2% to 3%) of iron is present within heme and nonheme proteins and enzymes, and a tiny proportion (< 0.2%) is bound to the transport protein transferrin.[10] Iron is essential for cell metabolism and growth, and is distributed between 3 compartments in the cell: the transit pool, the storage pool, and the functional pool. The intracellular transit pool is often called the "labile iron pool," and its exact chemical nature remains uncertain, although it has been suggested that iron(II)glutathione is a dominant component of this pool.[11] The main storage compartment is cytosolic ferritin, from which iron can be mobilized as and when required. The functional iron pool can be divided into extramitochondrial and mitochondrial functional iron, the organelle in which heme synthesis and iron-sulfur protein synthesis occur.

The same properties that enable iron to be an

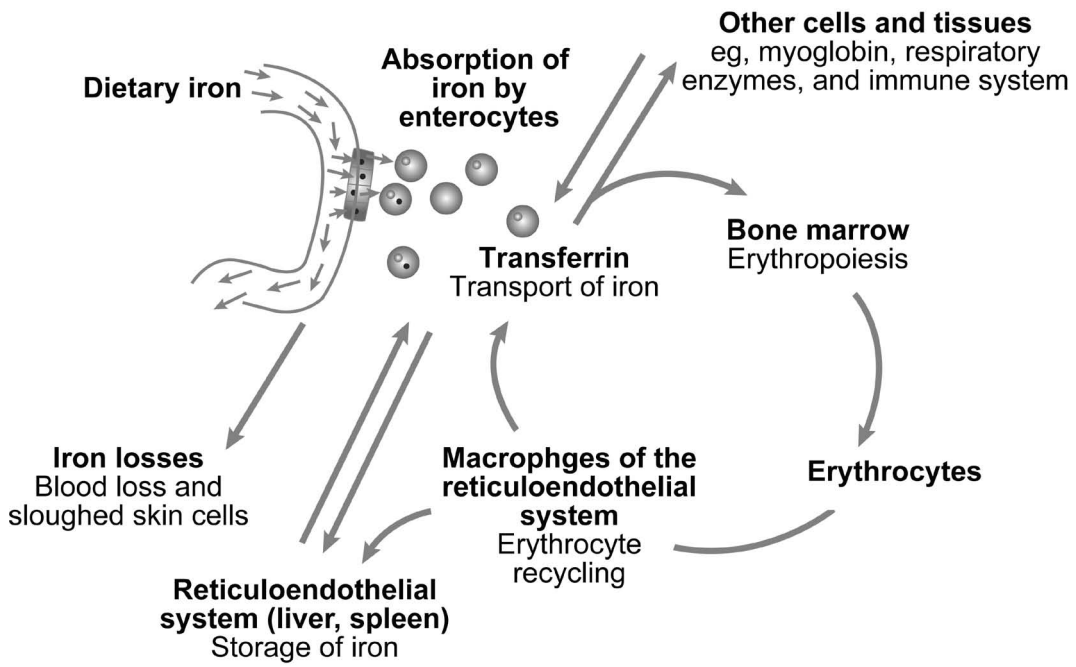

Figure 1. The metabolism of iron.

efficient cofactor in controlled redox reactions are also responsible for its toxicity. Under physiological conditions, iron mainly exists in 2 valence states: Fe^{2+} (ferrous) and Fe^{3+} (ferric). Cycling between the two states can lead to formation of reactive oxygen species (ROS) and thus oxidative stress. Iron is therefore highly regulated within the body, transported and stored tightly bound to iron-specific proteins in a nonredox active form. Iron in food exists largely as Fe^{3+}, which upon reduction to Fe^{2+} by a membrane reductase and subsequent transport through the enterocyte membrane, is oxidized back to Fe^{3+} after being exported out of the enterocytes. Ferric is tightly bound to the transport protein transferrin in the plasma for delivery to the tissues (Figure 1).[12] Iron is primarily stored in the form of ferritin in the liver and in the reticuloendothelial system.

Under normal circumstances, iron uptake from the gut is tightly regulated and transferrin is only approximately one-third saturated.[3] Thus, the levels of nontransferrin bound iron (NTBI), a form of iron that might induce oxidative stress (see next section), are kept undetectably low.

IRON THERAPY

Oral Versus Parenteral Iron Therapy

Iron supplementation can replenish iron stores effectively in the majority of patients where dietary intervention is inadequate. Oral iron supplements, particularly ferrous salts, are frequently prescribed in response to iron-deficiency anemia or iron deficiency. Although inexpensive and convenient, oral iron therapy has several important limitations (Table 1). First, interactions with foodstuffs can lead to precipitation of Fe^{3+} in the gastrointestinal tract, especially at high doses (2 to 3 times 60 or 100 mg iron). The oxidation of Fe^{2+} to Fe^{3+} can lead to formation of ROS, provoking local oxidative damage at the mucosal boundary and local toxicity in the gut with symptoms such as vomiting, dyspepsia, diarrhea, and heartburn. Such adverse effects contribute to widespread noncompliance with iron salt supplement regimens. Second, the efficacy of oral iron salts is limited by poor absorption of iron from the gastrointestinal tract, a problem that is exacerbated by various well-recognized interactions with drugs such as proton pump inhibitors, tetracyclines, and phosphate binders.[13] This problem is compounded by inhibition of iron uptake and export from the enterocytes to the plasma due to elevated hepcidin levels in patients with chronic inflammation.[14] Taking iron salts with food inhibits absorption further, which is unfortunate since concomitant food can ameliorate gastrointestinal side effects.

Finally, passive and uncontrolled diffusion of Fe^{2+} from the gut directly into the blood can occur following administration of high doses of oral ferrous salt preparations.[15] This, in turn, can lead to high

Table 1. Characteristics of Oral Ferrous Salts Versus Intravenous Iron Therapy

Characteristic	Oral Iron	Intravenous Iron
Intestinal absorption	• Impaired by concomitant food (depending on formulation) • Impaired by concomitant medication (eg, phosphate binders, gastrointestinal medications that reduce acidity) • Iron uptake and export of iron from enterocytes via ferroportin inhibited by elevated hepcidin levels	• Parenteral administration
Iron bioavailability	• May be inadequate during ESA therapy (accelerated erythropoiesis)	• Generally high
Safety	• Gastrointestinal adverse events affect a high proportion eg, constipation, dyspepsia, bloating, nausea, diarrhea, heartburn • Most frequent with ferrous sulfate	• Good safety profile Risk of (rare) anaphylaxis with dextran-containing formulations Risk of (rare) hypersensitivity reactions
Oxidative stress	• Can saturate the iron transport system if the iron is rapidly released (eg, ferrous sulfate), resulting in oxidative stress	• Oxidative stress only observed with less stable preparations which can release some more "weakly-bound" iron (eg, sodium ferric gluconate, iron sucrose similars) than stable (robust) iron complexes (eg, ferric carboxymaltose, originator iron sucrose)
Compliance	• Pill burden: usually 3 tablets per day • Affected by gastrointestinal intolerance	• Administered by health care professional
Convenience	• Administered at home	• Requires clinic visits
Cost	• Inexpensive	• More expensive per dose but fewer doses required

levels of transferrin saturation, and thus, formation of significant amounts of NTBI (often also called "free iron") in the plasma.[16,17] The NTBI is taken up from the plasma in an unregulated manner by cells in the endocrine system, the heart and other tissues, where it can catalyze the formation of ROS, and thus induce oxidative stress.[18-20] The Fe^{2+} and Fe^{3+} iron redox cycling pair catalyzes redox conversion of the relatively harmless oxygen products superoxide anion and hydrogen peroxide into the highly reactive hydroxyl radical. The reaction between Fe^{2+} and hydrogen peroxide is also called the *Fenton reaction*.[17] Hydroxyl radicals can damage a wide range of biological macromolecules in the immediate vicinity.[21] The NTBI can increase the intracellular labile iron pool,[20] which can thus initiate a chain of reactions that result in lipid peroxidation, membrane disruption, DNA strand breakage, and immunological disturbances (Table 2).[10]

Stable non-ionic ferric iron complexes, such as the Fe^{3+} polymaltose complex (Maltofer), have been developed for oral use. These complexes are able to avoid the risk of toxicity seen with iron salts[22,24,33] and show improved gastrointestinal tolerability compared to iron salts,[33] as well as permit ingestion with food.[34] Even with stable oral complexes, however, the bioavailability of iron from oral supplements is low and thus they must often be taken for 2 to 3 months even after correction of anemia has been achieved in order to replenish the body's iron stores. Moreover, oral iron is often inadequate to meet the demand for iron during treatment with an ESA.[1]

Parenteral administration bypasses the absorption difficulties associated with oral iron, even in the presence of elevated hepcidin levels,[35] such that hemoglobin concentration and iron parameters, increase more quickly than with oral iron.[36-38] Parenteral iron is an appropriate option in CKD patients with severe iron deficiency or deficiency that proves unresponsive to oral iron therapy,[39] or in patients receiving ESA therapy, particularly if there is a lack of response, or those undergoing hemodialysis.

Parenteral iron preparations have evolved dramatically since the first toxic injections of iron-oxyhydroxide complex in the 1930s.[40] A series of iron complexes has been developed for intravenous use, in which various carbohydrate ligands stabilize the iron core, ie, a polynuclear, non-ionic Fe^{3+}-oxyhydroxide core similar to that of the physiological iron storage protein ferritin. The first such complex, saccharated iron oxide, now more commonly known as "iron sucrose," was introduced by Nissim and Robson[41] and as Ferrum Hausmann Intravenous by Hausmann Laboratories (now Vifor Pharma) in 1949 in Switzerland. This preparation is today produced by Vifor Pharma under the brand name Venofer®. Later, Imferon®, a low-molecular-weight iron dextran became available in 1954. It was followed by other low-molecular-weight iron dextrans (INFeD®, CosmoFer®) and a high-molecular-weight dextran (Dexferrum®), ferric gluconate (Ferrlecit®), ferric citrate (Jectofer®), and more recently, ferric carboxymaltose (Ferinject®), iron isomaltoside 1000 (MonoFer®), and ferumoxytol (Feraheme®, Rienso®).[40] The latest generation of intravenous iron preparations (ferric carboxymaltose, iron isomaltoside 1000, and ferumoxytol) permit administration of a much higher dose of iron in a single administration without the need for a test dose. Additionally, a shift from intramuscular to intravenous administration has been welcomed by patients.

Table 2. Potential Oxidative Effects of Iron

Target	Effect	Potential Implications
Lipids	Catalyzes the oxidative degradation of lipids, resulting in a chain reaction of lipid peroxidation[22,23] in cell membranes, fibroblasts and macrophages.[10] Mitochondria are particularly susceptible to lipid peroxidation.[24,25]	Range from changes in membrane permeability to cell lysis. Oxidation of low-density lipoprotein cholesterol promotes atherosclerosis.
DNA	Dose-related damage to DNA constituents,[10,26] possibly potentiated by ascorbic acid (vitamin C)[27]	Single-strand breaks, base lesions, sugar lesions, abasic sites and DNA-protein cross links.
Immune system	Less well understood, but some oral iron preparations (eg, iron protein-succinylate,[28] iron citrate[29] and ferrous sulfate[30]) can impair the immunological profile, affecting various immune cell populations.[10]	Low immunological defense can potentially lead to higher infection rates.[31]
Gastric mucosa	Damage to the gastric epithelium[32]	Gastric ulceration and erosions, leading to gastrointestinal side effects

Physicochemical Characteristics of Intravenous Iron Preparations

The physicochemical properties of the iron complexes used for intravenous iron therapy (Table 3) determine which ones are best suited for parenteral use and offer the lowest toxicity. In particular, the thermodynamic stability of the complexes defines the amount of "weakly-bound" iron present in the intravenous iron formulation and thus the extent of iron that is directly transferred to transferrin. The thermodynamic stability thus restricts the maximum amount of a preparation that can be given in a single dose and the rate of its administration, without formation of large amounts of NTBI (Table 4).

Another important physicochemical parameter is the reduction potential, ie, the propensity of the complex to be reduced and thus induce oxidative stress. In the most stable compounds (eg, iron dextran, ferric carboxymaltose, and ferumoxytol), the polynuclear iron core cannot be reduced under physiological conditions to $Fe^{2+}$by naturally occurring reducing agents such as ascorbic acid or reduced nicotinamide adenine dinucleotide phosphate (NADPH), minimizing the risk of oxidative stress reactions.[24] Less stable preparations such as iron gluconate are more prone to reduction.

Toxicology Studies and Iron-induced Oxidative Stress in Nonclinical Models

Nonclinical toxicology studies with high iron doses have shown that iron-related pathological changes are observed first in the liver,[46] where cells become infiltrated by iron, causing necrosis. Subsequently, necrotic changes in organs such as the heart, brain, adrenal glands, kidney, spleen, and lungs start to become apparent.[24]

Studies with nonanemic rats have shown that there are significant differences in oxidative stress and inflammation levels induced by the different intravenous iron preparations–even between stable complexes that release negligible amounts of iron directly into the circulation.[47-49] Following 5 weekly doses of 40 mg iron per kilogram of body weight, increased levels of markers of oxidative stress and inflammation were observed in animals treated with sodium ferric gluconate, iron dextran, ferumoxytol, or iron isomaltoside 1000 compared to animals given ferric carboxymaltose or iron sucrose.[47-49] This was coupled with physiologic effects of hypotension and impaired liver and kidney function.

Due to the complex manufacturing process involved in the production of polynuclear Fe^{3+} oxyhydroxide compounds, in particular iron sucrose, iron sucrose similar formulations may not show identical physicochemical properties and toxicity profiles as those of the originator drug. Several nonclinical studies have reported that oxidative stress and inflammation vary between different iron sucrose similar preparations compared to the originator drug (Venofer®).[50-53] In the same rat model as that described above, oxidative stress and inflammatory responses in the liver, heart, and kidneys were significantly higher in animals receiving various iron sucrose similars versus the originator, accompanied by reduced kidney function

Table 3. Physicochemical and Pharmacokinetics Parameters for Intravenous Iron Preparations[42,43]

Parameter	Ferumoxytol (Feraheme®)	Iron Dextran (Imferon®) USP/BP	Ferric Carboxymaltose (Ferinject® or Injectafer)	Iron Isomaltoside (MonoFer®)[42]	Iron Sucrose (Venofer®)	Sodium Ferric Gluconate in Iron Sucrose Solution (Ferrlecit®)
Molecular weight, Da	185 000* 731 000† 275 700‡	103 000* 410 000† 165 000‡	150 000* not measured† 233 100‡	69 000* not measured† 150 000‡	43 300* 252 000† 140 100‡	37 500* 200 000† 164 100‡
Reactivity	Low	Low	Low	Low	Moderate	High
Half life, h	14.7	27 to 30	7.4/9.4¶	23.2[44]	5.3	1.42
C_{max}, mg Fe/L	130	…	37/331¶	37.3	35.3	20.6
Area under the curve, mg Fe/L × h§	922	1371	333/6277¶	1010	83.3	35.0
Clearance, L/h	0.11	…	0.26/0.16¶	0.10	1.23	2.99

*Method based on the USP Iron sucrose injection, relative to a pullulan standard, as reported in Geisser and colleagues[24]
†Method according to Balakrishnan and colleagues,[45] relative to a protein standard
‡Method according to Jahn and colleagues,[42] relative to dextran standards
§Standardized for a dose of 100 mg of iron
¶For Ferinject®, the second PK-values represent the results from the clinical study with a dose of 1000 mg of iron.

Table 4. Dosing and Administration of Intravenous Iron Preparations According to Manufacturers' Recommendations

Preparation	Maximum Single Dose	Minimum Duration of Infusion or Injection	Test Dose Required	Postdose Observation Required
Ferric carboxymaltose (Ferinject®*)				
Infusion	Up to 1000 mg iron in a single dose* (maximum 20 mg Fe/kg), or 200 mg in hemodialysis patients	100 mg to 200 mg iron, no minimum ≥ 200 mg to 500 mg iron, 6 min ≥ 500 mg to 1000 mg iron, 15 min	No	No
Injection	Up to 1000 mg iron in a single dose* (maximum 15 mg Fe/kg)	100 mg to 200 mg iron, no minimum ≥ 200 mg to 500 mg iron, 100 mg Fe/ min ≥ 500 mg to 1000 mg iron, 15 min	No	No
Ferumoxytol (Feraheme®)				
Injection	510 mg iron followed by a second 510 mg iron injection 3 to 8 days later	17 s (30 mg Fe/s)	No	Yes (minimum 30 min)
Iron isomaltoside (Monofer®)				
Total dose infusion	20 mg Fe/kg	0 mg to 10 mg Fe/kg, 30 min 11 mg to 20 mg Fe/kg, 60 min	No	No
Drip infusion	200 mg to 1000 mg Fe per week	0 to 5 mg Fe/kg, 15 min 6 to 10 mg Fe/kg, 30 min 11 to 20 mg Fe/kg, 60 min	No	No
Injection	100 mg to 200 mg iron up to 3 times a week	50 mg Fe/min	No	No
Iron dextran (Cosmofer®/ InFed®)				
Total dose infusion	20 mg Fe/kg	4 to 6 h	Yes	Yes (minimum 1 h after total dose infusion)
Drip infusion	20 mg Fe/kg	15 min for first 25 mg iron, wait 15 minutes, administer remainder at minimum 20 min/dL solution	Yes	No
Injection	20 mg Fe/kg	Administer 25 mg Fe over 1 to 2 min, wait 15 min, administer remainder	Yes	No
Iron sucrose (Venofer®)				
Infusion	100 mg to 400 mg iron (500 mg iron in some markets)	100 mg, 15 min 200 mg, 30 min 300 mg iron, 1.5 to 2.5 h 400 mg iron, 2.5 h 500 mg iron, 3.5 h	Yes/No†	Only in some markets (eg, USA, minimum 30 min)
Injection	100 mg to 200 mg iron	5 to 10 min	Yes/No†	Only in some markets (eg, USA, minimum 30 min)
Ferric gluconate in sucrose solution (Ferrlecit®)				
Infusion	125 mg iron (or 62.5 mg iron in some markets)	1 h	No	Yes (minimum 30 min)
Injection	125 mg iron	12.5 mg Fe/min	No	Yes (minimum 30 min)

*Injectafed® in some markets. See Ferinject® prescribing information for dosing limitations.
†Varies between markets.

and hepatic damage.[51-53] Three cases of adverse events following conversion to an iron sucrose similar have been described in the literature.[54] In a sequential, observational study undertaken at a single center in France, 75 hemodialysis patients exhibited a significant decrease in hemoglobin level despite a higher dose of intravenous iron and ESA therapy following conversion from iron sucrose (Venofer®) to an iron sucrose similar preparation.[55]

Dextran-related Toxicity

Iron complexes that contain dextran ligands can

cause dextran-induced anaphylactic reactions, albeit rarely.[56] Low-molecular-weight iron dextran has been associated with severe anaphylactic events, but at a far lower rate than high-molecular-weight formulations.[57,58] Nevertheless, the risk of these serious acute reactions has led to recommendations that intravenous iron dextran should be avoided.[7] Complexes that do not contain dextran, of course, cannot induce such reactions although nondextran induced hypersensitivity reactions are still possible.

Sodium ferric gluconate, iron sucrose, and ferric carboxymaltose do not contain dextran or any dextran derivatives and thus do not cross-react with antidextran antibodies in vitro.[59] In ferumoxytol, the ligand is carboxymethyl dextran, a dextran derivative.[42] The ferumoxytol prescribing information requires that patients must be observed for signs and symptoms of hypersensitivity for at least 30 minutes after its administration. One case of laboratory-proven anaphylaxis related to ferumoxytol has been reported in a patient with a previous reaction to iron dextran.[60] The ligand in iron isomaltoside 1000 is a very-low-molecular-weight hydrogenated dextran (3 to 5 glucose units) which has been shown to cross-react with antidextran antibodies in vitro,[59] possibly because it may act as a polyvalent dextran when it is bound to the polynuclear iron core. Although the isolated ligand is not immunogenic, iron isomaltoside 1000 should be used with caution in patients who have experienced a previous anaphylactic reaction to iron dextran. Clinical data show, however, that iron sucrose can be administered to patients with a previous reaction to iron dextran.[61-64]

Reliable clinical evidence regarding the relative incidence of hypersensitivity reactions to different intravenous iron preparations is difficult to obtain since the absolute rates of occurrence are low and reporting tends to be poor. Additionally, pharmacovigilance data from drug authorities are inevitably skewed in favor of older products, due to the tendency of prescribers to more actively report adverse events related to more recently available preparations (the *Weber effect*). Analyses of data from the Food and Drug Administration have shown a higher risk of anaphylaxis for low-molecular-weight iron dextran versus sodium ferric gluconate or iron sucrose,[65] as would be expected, and for ferumoxytol versus sodium ferric gluconate or iron sucrose.[66] However, due to the inherent bias in spontaneously reported pharmacovigilance systems of this type, the value of performing such analyses, as well as the clinical significance of such reports, remains questionable.

Pharmacokinetics and Pharmacodynamics of Intravenous Iron Preparations

Stable complexes such as iron dextran, ferric carboxymaltose, iron isomaltoside 1000, and ferumoxytol show longer terminal elimination rates than iron sucrose,[67] which in turn is eliminated more slowly than sodium ferric gluconate (Table 3). When standardized, dose-normalized values of the area under the concentration-time curve are compared, it can be seen that area under the curve is largely determined by the terminal elimination rate, ie, there is a negative correlation between the area under the curve and the elimination rate constants (Figure 2).

The bioavailability of iron from intravenous iron preparations, defined as the "the rate and extent to which the active substance or active moiety is absorbed from a pharmaceutical form and becomes available at the site of action,[68]" cannot be assessed simply by measuring plasma concentrations of iron since iron is present throughout the body, is constantly in flux between different compartments, and is transported in the plasma bound to iron-specific proteins. Moreover, the key site of action for exogenous iron is the erythrocyte, so plasma concentrations are not biologically relevant. The optimal technique for assessing iron bioavailability is to label the iron

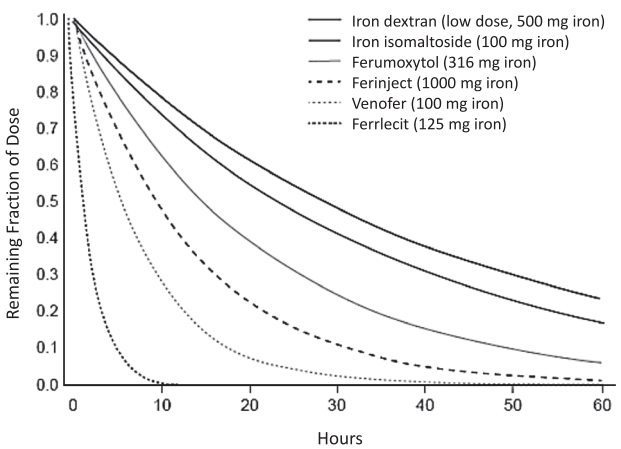

Figure 2. Dose-normalized simulated single first-order elimination kinetics for intravenous iron preparations, depicted as fraction of total serum iron over time (adapted from reference 43).

in the complexes with radioactive or stable iron isotopes and measure uptake in the erythrocytes.[69] Using this technique, Beshara and colleagues have shown that utilization of iron by erythrocytes following a single intravenous administration of iron sucrose[70] or ferric carboxymaltose[71] is within the range of 91% to 99% in patients with iron-deficiency anemia. Comparable data are not available for other intravenous iron products.

Dosing and Indications for Current Intravenous Iron Preparations

As discussed above, the physicochemical characteristics, and thus the type of ligands of iron complexes used for intravenous therapy, determine the maximum dose and administration times. Stable complexes that do not contain dextran or dextran derivatives, such as ferric carboxymaltose, can be administered rapidly in large doses since the risk of oxidative stress is lower than with smaller, less robust complexes.[47] The opportunity to administer large single doses with the newest preparations may reduce the need for total dose infusions, thereby avoiding the risk of iron overload and side effects such as arthralgia in patients for whom the amount of iron required to replenish stores is very high (eg, 2000 mg iron). Instead, 2 or even a single administration of ferric carboxymaltose, ferumoxytol, or iron isomaltoside 1000 may be adequate. Conventional dextran-based preparations require a test dose and must be administered slowly because they have the potential for a hypersensitivity reaction, even though they are large, stable complexes with tightly-bound iron and thus have a low risk of oxidative stress. Iron sucrose can generate significant amounts of NTBI if administered in high doses; therefore, the maximum recommended single dose is lower, and the administration time is longer, than for type I complexes (Table 4).[24] Sodium ferric gluconate (Ferrlecit®) releases relatively large amounts of iron directly into the circulation and is therefore administered slowly in small doses to limit the potential for acute liver toxicity due to NTBI-induced oxidative stress, as well as adverse events related to high transferrin saturation, eg, metallic taste.

Clinical Experience With Intravenous Iron Preparations in Kidney Disease

Iron supplementation is recommended for all CKD patients who receive ESA therapy, whether or not they require dialysis.[1] Dialysis-dependent patients usually have greater iron requirements than ND-CKD patients.[1] The European Renal Best Practice guidelines state that iron supplementation should be used first in any CKD patients with iron deficiency, and that only once iron stores are replete should ESA therapy be initiated.[72] The Kidney Disease Outcomes Quality Initiative recommends that iron supplementation should be given during ESA treatment to maintain minimum serum ferritin and TSAT levels in dialysis-dependent or nondialysis patients with CKD, with intravenous therapy the preferred route of administration in hemodialysis patients.[8] More recently, the Kidney Disease Improving Global Outcomes Clinical Practice Guideline for Anemia in CKD has suggested the potential for an increase in hemoglobin in patients with serum ferritin of 500 ng/mL or less and TSAT of 30% or less.[9]

Intravenous iron in dialysis-dependent patients. Several randomized trials have examined the efficacy and safety of different intravenous iron preparations in ESA-treated hemodialysis[73-76] and peritoneal dialysis[37,77] recipients with anemia (Table 5). Two of these studies compared intravenous iron (ferumoxytol or iron sucrose) versus oral iron as de novo therapy, and each found that the mean increase in hemoglobin was approximately twice as high with intravenous versus oral supplementation.[73,75] A comparison of sodium ferric gluconate in sucrose versus no iron in anemic hemodialysis patients showed similar but slightly less marked results which were still significantly in favor of the intravenous iron therapy, but in this cohort, baseline iron stores were relatively high (mean serum ferritin, 761 ng/mL).[74] Two other randomized trials have compared iron sucrose versus oral iron[37] or no iron[77] in anemic peritoneal dialysis patients receiving ESA therapy, and again, there was a significantly greater increase in hemoglobin in the intravenous iron-treated cohorts. No randomized studies have assessed the use of iron isomaltoside 1000 in CKD recipients, but in an 8-week noncomparative single-arm study for which safety was the primary endpoint, 182 patients (161 on dialysis and 21 not on dialysis) received either 4 intravenous bolus injections of iron isomaltoside 1000, 100 mg to 200 mg iron per dose, or, for 40 patients, a fast high-dose single

Table 5. Hemoglobin Response in Randomized Controlled Trials of Intravenous Iron in Dialysis Patients With Anemia

Study	Design	Population	Intravenous Iron Arm	Control Arm	ESA	Mean Hemoglobin Increase, g/dL		
						Intravenous Iron Arm	Control Arm	*P*
Provenzano et al 2009[73]	Multicenter Open label 5 weeks	230 hemodialysis patients	Ferumoxytol	Oral iron (ferrous fumarate)	Yes	1.02 ± 1.13	0.46 ± 1.06	< .001
Coyne et al 2007[74]	Multicenter Open label 6 weeks	134 hemodialysis patients	Sodium ferric gluconate	No iron	Yes	1.6 ± 1.3	1.1 ± 1.4	.03
Li et al 2008[75]	Single center Open label 8 weeks	136 hemodialysis patients	Iron sucrose	Oral iron (ferrous succinate)	Yes	3.77	1.79	< .05
Kosch et al 2001[76]	Single center Open label 6 months	59 hemodialysis patients*	Iron sucrose	Sodium ferric gluconate in iron sucrose	Yes	0.09[a]	0.09[a]	> .05
Singh et al 2006[77]	Multicenter Open label 8 weeks	96 peritoneal dialysis patients	Iron sucrose	No iron	Yes	1.3 ± 1.1	0.7 ± 1.1	.003
Li et al 2008[37]	Single center Open label 8 weeks	46 peritoneal dialysis patients	Iron sucrose	Oral iron (ferrous succinate)	Yes	3.38	0.68	< .05

*Maintenance phase, ie, all patients had received iron supplementation and erythropoiesis-stimulating agent (ESA) therapy prior to study entry (previous iron therapy was stopped 4 weeks before baseline)

infusion at baseline (in which the total calculated iron requirement was infused over 30 minutes, mean, 975 ± 238 mg iron).[78] In the 38 patients for whom iron isomaltoside 1000 was the first intravenous iron therapy, the mean hemoglobin increased by 1.20 g/dL by week 8.

There is also evidence that the addition of intravenous iron supplementation to ESA therapy reduces the ESA doses required by dialysis patients to achieve an adequate response,[75,77,79,80] with consequent cost savings, although ESA dose has not been the primary endpoint of any trial to date.

Safety data from randomized[37,73-77] and nonrandomized[78,81] studies indicate a low incidence of treatment-related adverse events in hemodialysis patients receiving intravenous iron therapy. Three randomized studies reported no adverse events related to intravenous iron therapy[37,75,76] or a similar incidence to that seen with oral iron (ferrous fumarate) or no iron,[73,74] with a low rate of treatment-related adverse events.[73,74,77] Only one serious adverse event with a suspected relation to intravenous iron therapy was reported, which was a case of hypotension in a patient receiving ferumoxytol that resolved within a few minutes.[73]

Given the efficacy and long-term experience with iron sucrose and its cost advantage versus new intravenous iron therapies, it is often used as first-line therapy in the hemodialysis setting since patients are already attending the unit frequently for dialysis sessions. While iron sucrose can only be administered in smaller doses than the newer generation of intravenous iron complexes (Table 4) and thus requires multiple dosing, this does not incur major inconvenience since specific clinical visits are not necessary and intravenous access is already established for the dialysis session. It should be noted, however, that iron sucrose similar preparations may not be therapeutically equivalent to the originator complex (Venofer®). In addition to preclinical data demonstrating a greater potential for toxicity with some iron sucrose similar preparations (see Toxicology Studies and Iron-induced Oxidative Stress in Nonclinical Models), there are preliminary data to suggest clinical differences.[51,55] In a sequential observational study of 75 ESA-treated hemodialysis patients who were switched from Venofer® to an iron sucrose similar, the mean levels of hemoglobin and TSAT decreased significantly in the 27 weeks after conversion compared to the preceding 27 weeks.[55] These alterations were seen despite a significant increase in the intravenous iron dose and a 13.8% increase in ESA dose after the switch as physicians attempted to maintain hemoglobin levels at the pre-conversion level. One center has described the onset of adverse events, including severe hypovolemic dysregulation, after conversion

of 3 patients from Venofer® to an iron sucrose similar.[51] Controlled clinical trials of iron sucrose similars would appear warranted before their widespread adoption.

Intravenous iron in nondialysis chronic kidney disease patients. All but one randomized study of intravenous iron versus oral iron (ferrous sulfate or ferrous fumarate) in ND-CKD patients have shown a significantly greater erythropoietic response in the intravenous iron treatment arms (Table 6). A hemoglobin increase of at least 1 g/dL has been observed in 50% to 100% more patients randomized to intravenous iron versus oral iron,[38,82,84] representing a clinically relevant difference. The tolerability of intravenous iron appears to be at least as good, or better, than that of ferrous sulfate or ferrous fumarate in this setting, and serious drug-related adverse events are rare in ND-CKD patients receiving intravenous iron within randomized studies.[38,82-84]

A question of particular interest is whether iron supplementation alone can produce an adequate increase in hemoglobin without ESA therapy, a situation that would be desirable both in terms of cost and the avoidance of ESA-related side effects. There is an increasing body of evidence to indicate that intravenous iron can avoid, or at least delay, the need for ESA in some ND-CKD patients.[85] In one randomized trial by Agarwal and colleagues, 75 ND-CKD patients were randomized to sodium ferric gluconate or oral iron (ferrous sulfate) without concomitant ESA therapy.[83] The increase in hemoglobin from baseline to the end of the 6-week study was significant in the intravenous iron group but not in the oral iron arm. Subpopulation analyses of data from three large randomized studies have been performed among the patients without ESA therapy, each of which showed a significantly greater hemoglobin response among intravenous iron-treated patients versus those randomized to oral iron (Table 7).[38,82,84] Of note, in one randomized trial, the proportion of patients achieving an increase in hemoglobin of at least 1g/dL was similar with ferric carboxymaltose and no ESA (53.2%) versus oral iron (ferrous sulfate) given in combination with ESA therapy (50.0%; Figure 3).[82] Consistent with this, in a series of 30 ND-CKD patients who showed a mean

Table 6. Hemoglobin Response in Randomized Trials of Intravenous Versus Oral Iron in Nondialysis Chronic Kidney Disease Patients

Study	Design	n	Intravenous Iron Arm	Oral Iron Arm	ESA	Mean Hemoglobin Increase, g/dL		
						Intravenous Iron Arm	Oral Iron Arm	*P*
Qunibi et al 2011[82]	Multicenter Open label 8 weeks	255	Ferric carboxymaltose	Ferrous sulfate	Yes/No	0.95 ± 1.12	0.50 ± 1.23	.005
Spinowitz et al 2008[38]	Multicenter Open label 5 weeks	304	Ferumoxytol	Ferrous fumarate	Yes/No	0.82 ± 1.24	0.16 ± 1.02	< .001
Agarwal et al 2006[83]	Multicenter Open-label	75	Sodium ferric gluconate	Ferrous sulfate	No	0.4 ± 0.8	0.2 ± 0.9	> .05
Van Wyck 2005[84]	Multicenter Open label 7 weeks	188	Iron sucrose	Ferrous sulfate	Yes/No	0.7	0.4	.01

Table 7. Hemoglobin Response in Randomized Trials of Intravenous Versus Oral Iron in Nondialysis Chronic Kidney Disease Patients not receiving Erythropoiesis-stimulating Agent Therapy

Study	Design	n	Intravenous Iron Arm	Oral Iron Arm	Mean Hemoglobin Increase, g/dL		
					Intravenous Iron Arm	Oral Iron Arm	*P*
Agarwal et al 2006[83]	Multicenter Open label	75	Sodium ferric gluconate	Ferrous sulfate	0.4 ± 0.8†	0.2 ± 0.9	> .05
Qunibi et al 2011[82] and Benjamin 2009[86]*	Multicenter Open label 8 weeks	188*	Ferric carboxymaltose	Ferrous sulfate	1.16 ± 1.1	0.75 ± 1.1	.01
Spinowitz et al 2008[38]*	Multicenter Open label 5 weeks	188*	Ferumoxytol	Ferrous fumarate	0.62 ± 1.02	0.13 ± 0.93	.005
Van Wyck 2005[84]*	Multicenter Open label 7 weeks	161*	Iron sucrose	Ferrous sulfate	0.7	0.4	.03

*Subpopulation analysis
†*P* < .01 versus baseline

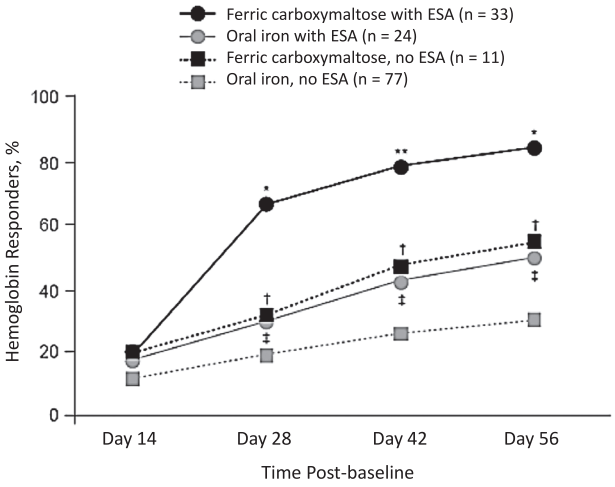

Figure 3. Proportion of hemoglobin responders (defined as subjects with hemoglobin increase ≥ 1 g/dL on or before each visit) among nondialysis patients with chronic kidney disease randomized to ferric carboxymaltose or oral iron (ferrous sulfate), with or without concomitant erythropoiesis-stimulating agent (ESA) therapy (adapted with permission from reference 86).
*P < .001
**P < .01 for ferric carboxymaltose with ESA versus ferric carboxymaltose with no ESA
†P > .05 for ferric carboxymaltose with no ESA versus oral iron with ESA
‡P > .05 oral iron with ESA versus oral iron with no ESA

hemoglobin increase of 0.73 g/dL 1 month after a single infusion of ferric carboxymaltose (800 mg iron), there was no difference in the hematopoietic response between patients with (n = 6) or without (n = 24) concomitant ESA therapy.[87]

These studies, however, were all of relatively short duration (maximum 8 weeks). Data to 1 year are available from a single-arm trial that evaluated the effect of intravenous iron supplementation (iron sucrose) in a series of 60 ND-CKD patients with anemia who were not receiving ESA therapy.[88] Although the mean TSAT level in the study population was 21.6%, the mean serum ferritin level was 98 ng/mL, below recommended minimum levels. Encouragingly, there was a significant increase in the mean hemoglobin of 1.6 g/dL from baseline to the 12th month. The most marked increase was observed over the first 6 months after the start of treatment, but was sustained and increased further to the 12th month.[89] Comparative 1-year data on the impact of intravenous iron in the absence of ESA therapy in ND-CKD patients will be provided by the ongoing FIND-CKD study, in which 631 ND-CKD patients have been randomized to high-dose ferric carboxymaltose (targeting serum ferritin, 400 ng/mL to 600 ng/mL), low-dose ferric carboxymaltose (targeting serum ferritin, 100 ng/mL to 200 ng/mL), or oral iron (ferrous sulfate), in a 1:1:2 randomization schedule.[89]

CONCLUSIONS

There is a growing recognition that an adequate supply of iron is essential not only to avoid anemia but also to maintain a good quality of life, and it is becoming apparent that iron deficiency per se merits treatment even in nonanemic patients. The recent FAIR-HF trial randomized 459 iron-deficient patients with chronic heart failure, with or without anemia, to intravenous iron or oral iron and included quality of life as a primary endpoint.[90] Results showed that intravenous iron therapy improved quality of life in significantly more patients than oral iron even in the absence of anemia.[57] Growing awareness of the clinical impact of iron deficiency, coinciding with advances in the safety and convenience of new intravenous iron preparations, has resulted in a steady increase in intravenous iron use in CKD patients. Partly based on this experience, other therapeutic areas have seen a dramatic rise in intravenous iron supplementation, for example in cardiology, cancer-induced anemia, inflammatory bowel disease, and gynecology.

Physicians now have a wider choice of intravenous iron preparations than ever before. The structures of new preparations permit far larger doses of iron to be administered safely in a single visit, an important feature for ND-CKD patients in whom clinic attendance is required each time an intravenous iron dose is given. Careful attention to the dosing guidelines for individual compounds remains essential, since differences in physicochemical characteristics necessitate different maximum doses and rates of administration. Nevertheless, we now have the opportunity to achieve iron replenishment rapidly and conveniently in dialysis-dependent and ND-CKD patients.

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CONFLICT OF INTEREST

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