Safety in Iron Management

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• **Intravenous (IV) iron therapy has become an integral part of hemodialysis management during the past several decades, and the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative guidelines recognize that most patients undergoing hemodialysis will require IV iron therapy on a regular basis to reach target hemoglobin (Hgb) levels. There now are three IV iron compounds available in the United States: iron dextran, sodium ferric gluconate, and iron sucrose. Although all have been proven effective for increasing Hgb/hematocrit levels, recent data show differences in their relative safety profiles. During the past two decades, more than 30 deaths have been attributed to the use of IV iron dextran. The two newer compounds available in the United States, sodium ferric gluconate and iron sucrose, have more favorable safety profiles, with the largest prospective safety comparison to date showing sodium ferric gluconate to be similar to placebo in the incidence of serious anaphylactoid-type reactions. This article reviews safety data surrounding the IV iron therapies.** ***Am J Kidney Dis*** **41(S5):S18-S26.**

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ALL TREATMENT decisions that physicians make involve the weighing of risks and benefits, including nephrologists' treatment decisions involving the use of intravenous (IV) iron therapy. Benefits of IV iron therapy for hemodialysis patients are well established; IV iron is essential for enabling most iron-deficient hemodialysis patients to achieve target hemoglobin (Hgb) levels of 11 to 12 g/dL (110 to 120 g/L).[1] Correction of anemia may provide numerous benefits, including a significant decrease in left ventricular mass index and septal wall thickness; increased work capacity; improvements in fatigue, depression, and relationships; reduced hospitalization; and normalization of increased cardiac output.[2-6] Because iron is vital for normal energy use by cells and has an important role in oxygen delivery and overall health status, it is important for hemodialysis patients to maintain adequate levels of storage iron.

Both the European Anemia Best Practices Panel[7] and the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative guidelines in the United States[1] have conducted an analysis of risks versus benefits of IV iron therapy for the treatment of anemia. In each case, it was concluded that IV iron forms a cornerstone of hemodialysis therapy. Nevertheless, questions remain in some nephrologists' minds about the possible risks associated with IV iron therapy, including the risk for adverse reactions, cardiovascular disease (CVD), and infection. Much of the concern relates to problems of iron in its free-circulating form, in which iron can create reactive oxygen species that can result in inflammation, endothelial damage, and a potential increased risk for infection. This article discusses the evidence surrounding the potential risks of IV iron therapy.

ADVERSE REACTIONS TO IV IRON THERAPY

Good quantitative data from several analyses of adverse reactions to IV iron therapy have emerged during the past several years. Although a number of adverse reactions have been reported with the use of IV iron compounds, including injection-site reactions, diarrhea, and nausea,[8,9] reactions that pose the greatest danger to patients and thus are of greatest concern are anaphylactoid or allergic-type reactions. These are generally characterized by signs and symptoms that include urticaria, rash, dyspnea, hypotension, and, in the most severe cases, shock and death. The risk for anaphylactoid reactions appears to be greatest with IV iron dextran, probably because of the dextran component of the compound. High-molecular-weight dextran complexes alone are known to be antigenic even when not complexed to iron.[10] Possibly, the im-

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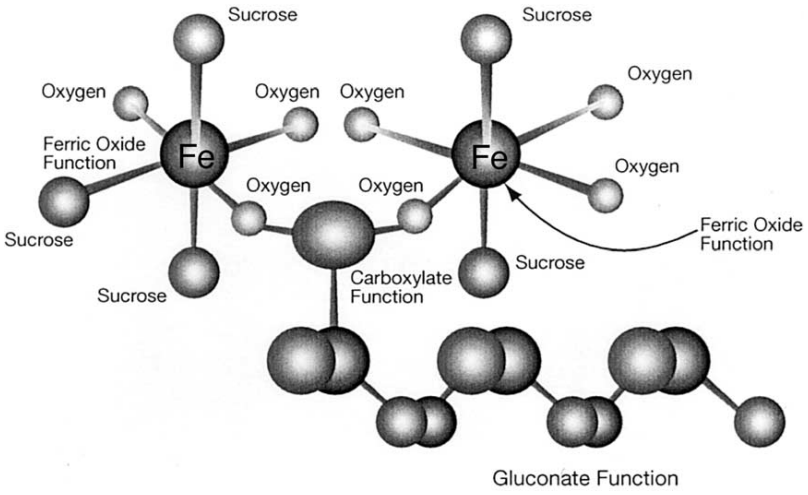

Fig 1. The molecular structure of sodium ferric gluconate consists of an iron core surrounded by saccharate networks, which are linked together by a gluconate function. The result is a stable complex of high molecular weight (289,000 to 440,000 d) that resists dissociation in serum and is nondialyzable. (Data from Watson Pharma, Inc.[13])

mune response is caused by a direct effect on mast cells and basophils.

The risk for immediate severe anaphylactoid reactions appears to be, at a minimum, approximately 0.6% with IV iron dextran, and this agent has been associated with a number of deaths during the past several decades. A 1980 review by Hamstra et al[11] examined the use of IV iron dextran in 481 hemodialysis patients administered a total of 2,099 doses of 250 or 500 mg. In this patient group, life-threatening reactions occurred in 3 patients (0.6%), characterized by respiratory arrest, hypotension, syncope, and wheezing. Eight additional patients had delayed nonlethal reactions that included myalgia, arthralgia, and pulmonary embolus. These data were borne out in later IV iron dextran studies by Woodman et al,[12] in which anaphylactoid reactions were seen in 1.8% of 1,260 patients, and by Fishbane et al,[9] in which such reactions were seen in 1.7% of 573 patients treated during a 2-year period.

Even with IV iron dextran, the expected risk for serious anaphylactoid reactions, approximately 6/1,000 patients, is relatively low, and the risk to the individual patient is low. However, the risk is far from negligible, and viewed in the context of a large hemodialysis practice that treats several hundred patients, it is likely that several severe reactions will be encountered over the course of time with IV iron dextran. Data by Faich and Strobos,[10] published in 1999, have illustrated this significant risk for potentially fatal reactions. Using a database drawing on the US experience with IV iron dextran during a two-decade period (1976 to 1996), a total of 196 serious anaphylactoid reactions and 31 deaths were reported with the use of this compound. Among patients administered iron dextran who experienced allergic reactions, there was a minimum case fatality rate of 15.8%. (Because data from this study were drawn from retrospective reports, many of which did not list final outcomes, the actual case fatality rate may have been even greater.[10])

The two newer compounds introduced in the United States, sodium ferric gluconate and iron sucrose, appear to be associated with a far lower risk for anaphylaxis. This reduced risk appears to be related to the absence of dextran chains in these molecules; both compounds consist of a sucrose network surrounding a ferric ion core. In the case of sodium ferric gluconate, sucrose networks are linked by a gluconate function to create a highly stable nondialyzable macromolecular complex (Fig 1).[13]

This reduced risk has been shown in data published on sodium ferric gluconate. In 2002, Michael et al[14] published results of the largest prospective safety analysis conducted in hemodialysis patients. The study, which involved 2,493 hemodialysis patients, compared the rate of adverse reactions prospectively with placebo and with a historical control group of IV iron dextran users. Patients in this study were administered placebo or a 125-mg single dose of sodium ferric gluconate delivered by IV push at a rate of 12.5 mg/min during one session and then were crossed

over to the opposite treatment at the next session. The IV iron dextran comparison was drawn from four published trials involving 3,768 drug exposures to different forms of this compound.

The rate of life-threatening adverse reactions (immediate reactions requiring institution of resuscitative measures) was reduced from 0.61% in the IV iron dextran study population to 0.04% in the sodium ferric gluconate study population (~4/10,000 patients). The relative risk reduction was 93% (Table 1).[14] The single life-threatening reaction associated with sodium ferric gluconate consisted of shortness of breath, hypotension, and lower back pain. It resolved within 20 minutes, enabling the patient to complete the dialysis treatment and return home the same day.

In the placebo-controlled portion of this study, there was no significant difference in incidence of life-threatening reactions with sodium ferric gluconate compared with placebo (Table 2).[14] Although there was a statistically significant difference in incidence of drug-intolerance events (ie, any event that would preclude further study drug administration), most of these reactions consisted of lower-level gastrointestinal tract reactions.

Fewer safety data are available on the newest agent, IV iron sucrose. Unlike sodium ferric gluconate, iron sucrose has not been tested in a large-scale prospective study since its introduction in the United States. However, available data suggest a similar safety profile. In studies by Van Wyck et al[8] and Charytan et al[15] involving a total of approximately 1,000 doses of 100 mg of iron sucrose administered through IV infusion or push, no deaths and no potentially fatal anaphylactoid reactions were attributed to use of this compound. In the largest analysis of IV iron sucrose use, encompassing 1,004,477 patients worldwide from 1992 to 2001, a total of 788 adverse events were reported (incidence, 0.028%), including 52 anaphylactoid reactions. No deaths were reported.[16] Data for these two compounds strongly suggest that they are significantly safer than IV iron dextran in terms of serious adverse reactions, and the use of IV iron dextran should be restricted to selected patients in whom there is a particular need to treat with this compound.

Table 1. US Safety Study of Sodium Ferric Gluconate: Adverse Events for Sodium Ferric Gluconate Versus Iron Dextran

	Sodium Ferric Gluconate	Iron Dextran	*P*
Life-threatening	0.04, 1/2,493, 0.00-0.22	0.61, 23/3,768, 0.36-0.86	0.0001
Drug intolerance	0.44, 11/2,493, 0.21-0.71	2.47, 64/2,589, 1.87-3.07	<0.0001

NOTE. Comparison with iron dextran was taken from historical controls in published studies of iron dextran. Values expressed as percent, number/total number, 95% confidence interval.

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Table 2. US Safety Study of Sodium Ferric Gluconate: Adverse Events for Sodium Ferric Gluconate Versus Placebo

	Sodium Ferric Gluconate (N = 2,493)	Placebo (N = 2,487)	*P*
Life-threatening	1 (0.04)	0 (0)	Not available
Drug intolerance	11 (0.4)	2 (0.1)	0.02

NOTE. Values expressed as number (percent).

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CVD RISK

The link between CVD and IV iron therapy has good biological plausibility, at least in theory. Iron is an element with a high degree of acute-phase reactivity that can lead to a state of increased oxidative stress. Catalytically active iron is involved in the production of hydroxyl radical, a damaging reactive oxygen species. Hydroxyl radicals, in turn, lead to lipid peroxidation and the development of additional lipid-derived free radicals, which generate still other free radicals in a chain reaction.[17]

Most of the data associating iron with an increased risk for CVD have been drawn from population-based studies involving serum ferritin level as a measure of iron stores. A series of Finnish studies by Salonen et al[18-20] were among the first to test the "iron hypothesis" of an increased risk for CVD with increased iron stores. In these studies, an increased risk for myocardial infarction (MI) was found in men with greater serum ferritin levels compared with those with lower levels.[18] Subsequent studies by this same group showed that regular blood donors had a lower average serum ferritin level and decreased

risk for acute MI over time compared with non–blood donors.[19,20] A large-scale Canadian survey by Morrison et al[21] that followed up nearly 10,000 participants also showed an increased risk for fatal MI in those in the highest category of serum ferritin level (>175 μg/dL).

Nevertheless, it is exceedingly difficult to draw reasoned conclusions from these data about the risk for CVD in hemodialysis patients on IV iron therapy. First, these studies were population-based analyses that in most cases involved only male patients. An equal number of population-based studies that have examined the relationship between serum ferritin level and MI concluded there is no increased risk for CVD with greater iron stores and no protective effect with blood donation.[22-26]

Second, serum ferritin levels may not be a reliable marker for actual elevations in iron stores. Chronic inflammatory conditions, such as CVD, tend to elevate serum ferritin measures, making it questionable whether observational studies are measuring an increase in iron levels or results of an occult inflammatory process.

Third, such population-based studies also have not controlled for the presence of hemochromatosis, a hereditary disorder that results in massive accumulation of storage iron over a period of decades. Because this disorder is fairly common (1 of 300 Caucasians are homozygous for the Cys282Tyr mutation of HFE, one of the genes involved in hemochromatosis), failure to control for its presence may influence the outcomes of population-based analyses.

Finally, population-based studies involving body iron stores contribute little to our knowledge of the specific CVD risk associated with IV iron therapy in hemodialysis patients. The few studies to date conducted in the hemodialysis population tended to show a slight, but significant, increase in relative risk (~ 1.1 to 2.4).[27-29] However, this modest increase in risk must be weighed against the serious and well-documented health consequences of failing to correct iron-deficiency anemia in these patients.

RISK FOR INFECTION

Iron is crucial for survival in most organisms and is necessary for erythrocyte production and the making and storage of adenosine triphosphate. Oxidative phosphorylation, the production of usable energy, is highly dependent on iron. Therefore, the body strives to obtain iron and is very resistant to iron elimination. Of the estimated 4,000 mg of iron in the body, only approximately 1 mg/d is lost in healthy individuals. Nevertheless, the potent oxidizing ability of iron makes it a potentially toxic compound in the body in its free form. Because of this potential toxicity, the majority of iron that is not actively circulating as Hgb in red blood cells is safely sequestered in the form of ferritin and hemosiderin in macrophages of the reticuloendothelial system (RES). Molecules that hold iron tend to be very large, containing a central core of iron with a proteinaceous envelope that insulates the body from the iron atom (Fig 2). In healthy individuals, free iron rarely is a problem. Conversely, in cases of hemochromatosis, in which serum ferritin levels can increase to more than 10,000 ng/mL, the body is presented with unmanageable levels of free iron.

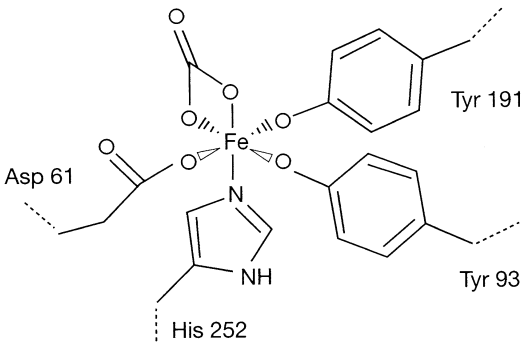

Fig 2. An iron-protein complex. Such complexes tend to be large glycoprotein complexes wrapped around a central core of iron that protects the body from exposure to free iron.

In hemodialysis patients on IV iron therapy, although iron is introduced directly into the circulation as opposed to the gastrointestinal tract, the body generally retains its ability to protect against free-iron release by taking up the iron-carbohydrate complex into the RES in its bound form. In the RES, iron is dissociated from its carbohydrate ligand, stored as ferritin or hemosiderin, and only then is turned over to transferrin, the body's primary serum buffer against free iron, for delivery to the erythroid marrow for use in Hgb production. A series of pharmacokinetic analyses by Seligman et al[30] and Kimko et al[31] showed that sodium ferric gluconate delivered at

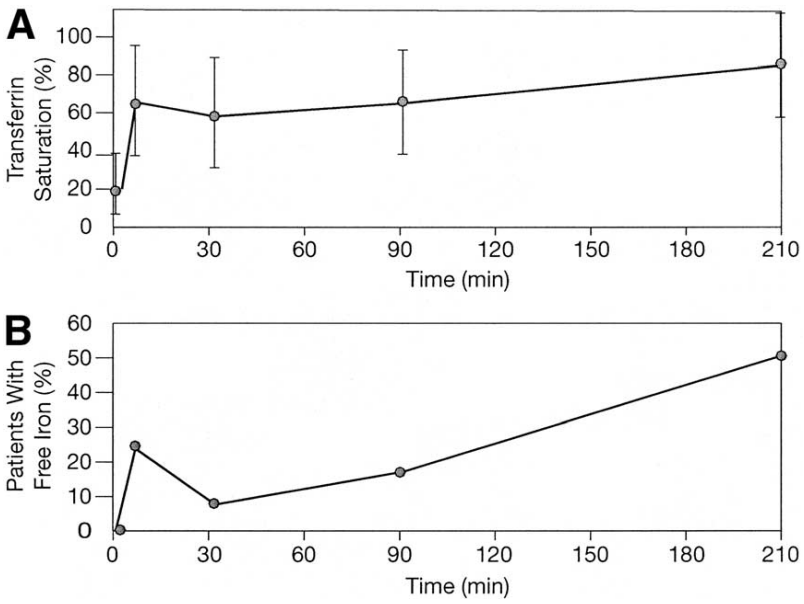

Fig 3. (A) Transferrin saturation and (B) percentage of patients with free iron after administration of iron sucrose, 100 mg, by IV push. Reprinted with permission.[33]

a dose of 125 mg by IV infusion or push follows this normal pathway of iron distribution. In these studies, the sodium ferric gluconate complex was taken up directly by the RES before being delivered back to transferrin. Release of free iron directly into the circulation was negligible, and no transferrin oversaturation was observed, even at an infusion rate greater than 15 mg/min. After the iron was taken up by the RES, turnover to transferrin was orderly: The majority of iron (~80%) was delivered back to transferrin and made available to the erythroid marrow within 24 hours of infusion.[30,31]

An increasing number of studies during the past 2 years have shown that the same protection against free-iron release may not be seen with IV iron sucrose. A pharmacokinetic study by Danielson et al[32] showed that iron sucrose follows two pathways after administration: Although part of the iron is transported directly to the RES in its carbohydrate-bound complex, a portion is released directly into the circulation, existing as nontransferrin-bound free iron. Subsequent studies have shown the potential detrimental effects of this method of iron release in terms of infection risk and oxidative damage. In 2000, Parkkinen et al[33] published results of an elegant series of studies on the release of free iron with iron sucrose and risk for infection. This study analyzed 12 stable hemodialysis patients with ferritin levels less than 400 ng/mL who received treatment with 100 mg of iron sucrose administered by IV push. Transferrin saturation was measured at 5, 30, 90, and 210 minutes postinjection, and serum iron was measured by means of two spectrophotometric methods using ferozine and ferene-S as the chromogenic agents.

Transferrin saturation increased rapidly immediately after injection (Fig 3A),[33] a phenomenon that would only occur if iron was moving directly to transferrin. Transferrin saturation continued to increase, averaging more than 80% within 3.5 hours. In addition, there was a consistent increase in number of patients with measurable free iron in the circulation as detected by bleomycin assay, climbing to 50% at 3.5 hours (Fig 3B).[33]

These findings have several clinical implications. First, patients with lower transferrin levels (which may occur in hemodialysis patients because of inadequate transferrin production in the liver) are likely at greater risk for having free iron in the circulation with IV iron sucrose. Second, the presence of free iron in the circulation may increase the risk for infection. This increased risk was shown by this group by introducing *Staphylococcus epidermidis* into serum samples in patients with free iron. Although *S epidermidis* normally does not grow in serum in the absence of free iron, the organism grew

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