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# AJKD

American Journal of  
Kidney Diseases

## IN-DEPTH REVIEW

### Iron Sucrose: The Oldest Iron Therapy Becomes New

Jerry Yee, MD, and Anatole Besarab, MD

• Several parenteral iron preparations are now available. This article focuses on iron sucrose, a hematinic, used more widely than any other for more than five decades, chiefly in Europe and now available in North America. Iron sucrose has an average molecular weight of 34 to 60 kd, and after intravenous (IV) administration, it distributes into a volume equal to that of plasma, with a terminal half-life of 5 to 6 hours. Transferrin and ferritin levels can be measured reliably 48 hours after IV administration of this agent. Iron sucrose carries no “black-box” warning, and a test dose is not required before it is administered. Doses of 100 mg can be administered over several minutes, and larger doses up to 300 mg can be administered within 60 minutes. The efficacy of iron sucrose has been shown in patients with chronic kidney disease (CKD) both before and after the initiation of dialysis therapy. Iron sucrose, like iron gluconate, has been associated with a markedly lower incidence of life-threatening anaphylactoid reactions and may be administered safely to those with previously documented intolerance to iron dextran or iron gluconate. Nonanaphylactoid reactions, including non-life-threatening hypotension, nausea, and exanthema, also are extremely uncommon with iron sucrose. Management of patients with the anemia of CKD mandates that we carefully examine the effectiveness and safety of this oldest of iron preparations and the accumulating present-day data regarding it and contemporaneous agents. *Am J Kidney Dis* 40:1111-1121.

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**INDEX WORDS:** Anaphylactoid reaction; chronic kidney disease (CKD); end-stage renal disease (ESRD); hemodialysis (HD); iron dextran; iron gluconate; iron sucrose.

**S**ENSING OF RENAL cortical hypoxia induces the elaboration of erythropoietin (EPO).<sup>1-3</sup> After EPO secretion, its presence in the developing erythron, along with other growth factors in bone marrow, maintains erythropoiesis, a process also regulated by the availability of iron. In patients with chronic kidney disease (CKD), red blood cell production may be mitigated not only by ongoing blood losses, but also by low-grade hemolysis and, to a variable degree, reticuloendothelial system blockade that often is attributed to cryptic inflammatory foci and inhibitory inflammatory cytokine actions.<sup>4-7</sup> In patients on chronic renal replacement therapy, iron must be administered by a parenteral route to replete iron stores to levels sufficient to maintain erythropoiesis. Although prevention of iron toxicity has proven to be one of the more formidable challenges facing today's caretakers of patients on dialytic therapy for end-stage renal disease (ESRD),<sup>8</sup> iron therapy of these patients,

to the extent possible, should never be in question because its fundamental presence is essential in the simplified balanced equation of EPO plus iron equals red blood cell production.

#### HISTORY OF INTRAVENOUS IRON USE IN DIALYSIS PATIENTS

Two products recently introduced in the United States after their respective approvals by the

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**Table 1. Iron Saccharate Formulations**

Brand Name	Pharmaceutical Name	Manufacturer	Country
Venofor	Iron hydroxide sucrose complex in water	Vifor International Inc	Switzerland
Ferrivenin	Iron saccharate	Laevosan	Austria
Fesin	Saccharated ferric oxide	Yoshitomi Pharmaceutical Co	Japan
Ferrum Vitis	Ferric saccharate	Neopharma	Sweden
Ferrum Lek	Saccharated ferric oxide and polymaltose complex	Lek Pharmaceuticals	Slovenia

Food and Drug Administration (FDA) represent new weapons in the therapeutic armamentarium that targets treatment of anemic patients with ESRD. These products represent alternatives to the most often used iron dextran formulations (INFeD; Watson Pharmaceuticals, Corona, CA; Dexferrum; American Regent Laboratories Inc, Shirley, NY). These products are sodium ferric gluconate complex in sucrose injection, also referred to as iron gluconate (Ferrlecit; Watson Pharmaceuticals), and iron sucrose, an iron hydroxide sucrose complex in water (Venofor; American Regent Laboratories). Both are as effective as iron dextran and less prone to induce an anaphylactoid reaction, presumably attributable to their lack of dextran moieties. Characteristics of iron gluconate have been reviewed recently by Fishbane and Wagner<sup>9</sup> and are not discussed in detail here.

Intravenous (IV) iron sucrose injection (Venofor) has been used successfully in Europe and is generally referred to in the European and world literature as iron saccharate or ferric saccharate. Several other products have been referred to as iron saccharate (Table 1). Some of these other saccharates have been withdrawn from the world market. The term iron saccharate is not used in the remainder of this review, and the term iron sucrose injection solely refers to the product called Venofor. Although iron sucrose has been used more widely than any other hematinic for five decades, it was introduced only recently to North America. This review focuses on the use of iron sucrose in CKD populations, principally those on dialysis therapy, and describes characteristics, therapeutic trials, potential uses, and safety of this preparation. Differences between characteristics of iron sucrose versus iron dextran or gluconate are commented on when applicable.

#### BIOCHEMICAL CHARACTERISTICS AND PHARMACOKINETICS

Iron sucrose is a water-soluble compound (pH 10.5 to 11.1; 1,430 mOsm/L) composed of a polynuclear ferric (III) hydroxide inner sphere surrounded by sucrose molecules.<sup>10,11</sup> It is devoid of iron ions, unlike the iron dextrans. The molecular weight of iron sucrose is 34 to 60,000 kd. Iron sucrose, like iron gluconate, is more readily bioavailable for erythropoiesis than iron dextran preparations. After the IV administration of iron sucrose, there is rapid distribution into plasma-binding proteins, primarily into apotransferrin and, to a lesser extent, ferritin.<sup>10</sup> Pharmacokinetic data do not address whether this rapid distribution of iron into plasma proteins results from direct donation to plasma proteins, chiefly transferrin, or from rapid intracellular processing of the iron sucrose moiety. The initial volume of distribution of iron sucrose equals that of iron dextran and is approximately equal to plasma.<sup>10</sup> A volume of distribution equal to plasma would be expected of an agent that does not donate directly to iron-binding proteins. In vitro observations by Van Wyck et al<sup>11</sup> suggest that iron dextran, iron gluconate, and iron sucrose may donate iron directly to transferrin.<sup>11</sup> Moreover, the degree of donation differs by agent and chemical class (iron gluconate > iron sucrose > iron dextran). Collectively, these data suggest that iron oversaturation was the source of dose-related reactions during IV administration of any of these compounds.

The alpha phase of elimination of an IV dose of iron sucrose is approximately 30 minutes, and its terminal half-life is 5 to 6 hours.<sup>10,12,13</sup> The terminal half-life of iron sucrose is nearly the same as that of the iron dextran marketed as INFeD,<sup>14</sup> which has a terminal half-life of nearly 6 hours. However, this terminal phase is slower

**Table 2. Comparison of Iron Preparation Formulations and Dosing**

	Iron Dextran	Iron Gluconate	Iron Sucrose
How supplied	100 mg/2 mL single-dose vial	62.5 mg/5 mL single-dose ampoule	100 mg/5 mL single-dose vial
Maximum infusion rate	20 mg/min	12.5 mg/min	20 mg/min
Total dose infusion (FDA approved)	No	No	No
Maximum dose/administration (not FDA approved)	500-1,000 mg over 4-6 hours	250 mg	500 mg

than that of iron gluconate,<sup>15</sup> which has a terminal half-life of approximately 60 minutes. The rapid disappearance of iron sucrose from plasma is associated with its distribution within minutes, assessed by positron emission tomographic scanning, into iron depots, including the liver and bone marrow.<sup>16</sup> Importantly, this iron sucrose uptake occurs without parenchymal damage because nearly all the iron is sequestered by reticuloendothelial cells, rather than parenchymal ones.<sup>17</sup> Changes in serum transferrin saturation (TSAT) and ferritin levels may be measured reliably just 48 hours after the IV administration of iron sucrose.<sup>18</sup> This is in contrast to iron dextran, in which slow and competitive delivery of complexed iron to endogenous plasma-binding proteins occurs during 3 to 4 days. Experiments *in vitro* have shown that dextran-bound iron may be liberated by the acidic assay conditions under which the test is performed, thereby precluding the validity of TSAT measurements for 1 or 2 weeks.<sup>19,20</sup>

Iron sucrose injection is supplied as Venofer in 5-mL vials that contain 100 mg of elemental iron. Each 100-mg vial may be administered undiluted by slow IV push over 5 minutes (20 mg/min) or as a 15-minute infusion in 100 mL of 0.9% sodium chloride (6 to 7 mg/min).<sup>21</sup> Others have administered iron sucrose as rapidly as 100 mg within 2 minutes (50 mg/min) without adverse effects.<sup>22</sup> By comparison, iron gluconate, supplied as 5-mL ampoules containing 62.5 mg of elemental iron, may be administered by IV push up to 125 mg over 10 minutes (12.5 mg/min) or as a 125-mg infusion in 100 mL of saline over 60 or more minutes ( $\approx$ 2 mg/min; Table 2).<sup>23</sup> Unlike the iron dextrans, it is not necessary to administer a test dose of either iron sucrose or gluconate during first-time administration, and the package inserts of

these compounds do not carry a “black-box” warning, a testament to the infrequency in which these non-immunoglobulin E mast cell-mediated reactions occur in association with these newer compounds.<sup>24,25</sup> In addition, the lack of requirement for test doses reduces hemodialysis (HD) facility costs while increasing patient caretaker time in other areas.<sup>26</sup>

#### EFFICACY

During 50 years of worldwide clinical experience, iron sucrose has been approved for use in 54 countries as hematinic therapy for a variety of disorders, ranging from the iron deficiency anemia of CKD to anemias associated with pregnancy and the postsurgical period.<sup>27,28</sup> Since November 2000, iron sucrose has been approved by the US FDA for the treatment of iron deficiency anemia in chronic HD patients administered supplemental EPO therapy.

In an early study of patients with CKD not on dialytic therapy who had been administered oral iron supplements to correct anemia, Silverberg et al<sup>29</sup> studied responses to the IV injection of iron sucrose in 33 patients. During a 6-month evaluation period during which no EPO was administered, 1 g of iron sucrose, administered as five monthly 200-mg IV doses, increased hemoglobin levels and hematocrits in 67% of those studied. These responses required approximately 3 months to develop. One third of patients did not respond to exogenous iron therapy, although TSATs and serum ferritin levels increased, implying that iron was not limiting erythropoiesis in these subjects. The investigators reaffirmed the relative lack of efficacy of oral iron and confirmed that EPO administration may not be required in all HD patients.<sup>30-32</sup> More recently, Stoves et al<sup>33</sup> reported that 300 mg of iron sucrose once each month was equivalent to 600

mg of ferrous sulfate in pre-ESRD subjects in terms of reducing the epoetin dose needed to attain and maintain target hemoglobin levels of 12 g/dL (120 g/L). This study emphasizes the difference in iron needs of pre-ESRD and ESRD patients. In the latter, oral iron is ineffective in the majority of cases because of ongoing dialysis-related losses that exceed the amount absorbed from 200 mg of elemental oral iron delivered through the gastrointestinal route.

Iron delivery may be the rate-limiting step in effective erythropoiesis in a variety of patients with ESRD on renal replacement therapy. To determine the frequency of this process, Silverberg et al<sup>34</sup> performed a complex 12-month study in a population of 9 continuous ambulatory peritoneal dialysis and 64 HD patients administered IV iron sucrose twice monthly as 100-mg infusions in 100 mL of saline. Patients were heterogeneous and subdivided into five groups, of which only the first two groups are germane to this discussion. Group 1 (N = 41 HD patients) had been administered epoetin at a constant dosage (average dose,  $98.8 \pm 27.7$  U/kg/wk) for 6 consecutive months preceding the initiation of IV iron therapy. During the evaluation period, which consisted of the next 6 months of iron therapy, this group's epoetin dose was adjusted as needed whenever the predialysis hematocrit decreased to less than 33%. Group 2 (N = 11 HD patients) patients were iron and epoetin naïve at the beginning of the study and were administered simultaneous iron and epoetin (average dose,  $95.6 \pm 23.2$  U/kg/wk) therapy for 6 months. During the second 6 months of the study, they received treatment as group 1.

By the study end, iron sucrose administration had decreased epoetin requirements in groups 1 and 2 by 61% ( $98.8 \pm 27.7$  to  $38.4 \pm 31.1$  U/kg/wk) and 76% ( $95.6 \pm 7.8$  to  $23.2 \pm 16.3$  U/kg/wk) over 6 months, respectively. Mean serum ferritin levels significantly increased in both groups. A mean hematocrit of 33.7% was achieved in patients administered iron sucrose with epoetin. The ultimate hematinic response (change in hemoglobin level or hematocrit) was not predicted by the initial serum ferritin or TSAT value, underscoring the notion that iron-limited erythropoiesis can only be definitively

diagnosed by iron therapy.<sup>8,35</sup> Although the magnitude of reductions in epoetin dosage in this study were greater than most of those reported for iron dextran,<sup>8,36</sup> no head-to-head comparison studies have been conducted to ascertain whether one agent is more efficacious than the other.

In an open-label, single-arm, prospective, multicenter study, Charytan et al<sup>18</sup> determined the efficacy of 10 consecutive 100-mg IV push doses of iron sucrose in 77 patients undergoing thrice-weekly HD. Subjects (mean hemoglobin level,  $10.3 \pm 0.2$  g/dL [ $103 \pm 2$  g/L]) had been administered epoetin for no less than 4 months and had not been administered oral iron for at least 2 weeks. This group monitored the more reliable parameter, hemoglobin level, rather than hematocrit.<sup>37</sup> Achievement of a hemoglobin level of 11 g/dL (110 g/L) was the principal outcome parameter. Efficacy analysis of 76 patients showed that 60 patients (78%) achieved the goal hemoglobin level at some point during the 60-day evaluation period, and the 300-mg dose of iron sucrose achieved a significant increase in hemoglobin level above baseline. Post hoc analysis showed that an entry TSAT less than 20% and an entry ferritin level less than 100 ng/mL (224.7 pmol/L) identified individuals who responded more vigorously to iron sucrose therapy. EPO doses were not reduced significantly because this parameter was held essentially constant throughout the study interval. As mentioned, iron indices were measurable reliably just 48 hours after completion of iron sucrose therapy.

Kosch et al<sup>38</sup> explored the possibility that once-monthly iron sucrose would be as effective as weekly iron gluconate in maintaining hemoglobin levels. They studied 55 stable epoetin-treated HD patients in a 6-month, open, randomized, prospective, controlled trial. A single 250-mg iron sucrose injection in 200 mL of 0.9% sodium chloride over 1 hour was administered monthly to 28 patients, whereas 27 patients were administered 62.5 mg of iron gluconate infused over a similar time weekly. By study end, the entry hemoglobin level of 11.3 to 11.4 g/dL (113 to 114 g/L) in all subjects remained stable on either regimen. Epoetin doses did not decrease in these stable iron-replete patients. However, serum ferritin levels and TSATs increased significantly with either agent. Ferritin levels increased from 412 to 650 ng/mL (926 to 1,461 pmol/L), whereas

TSATs correspondingly increased from 21.9% to 33.3% in the iron-sucrose group. These data compared favorably with those of the iron-gluconate group: ferritin levels increased from 369 to 650 ng/mL (829 to 1,461 pmol/L) and TSATs increased from 25.7% to 34.4%. Both regimens were deemed equally effective by the investigators. Of note, the accumulation of ferritin in both groups suggests that these regimens provided more iron than required to maintain a steady-state level of erythropoiesis. The corollary of this conclusion is that maintenance iron doses could have been lower than those provided.

Future studies are required to define optimal maintenance doses of the newer iron preparations; namely, doses that provide ample amounts of iron to the erythron, yet avoid unnecessary iron accumulation. A recent study by Fishbane et al<sup>39</sup> indicated that reticulocyte hemoglobin content more accurately identifies patients with functional iron deficiency than the more traditionally used indices of serum ferritin level or TSAT. Prospective studies are needed to determine the value of reticulocyte hemoglobin content in guiding maintenance iron therapy regimens. Assessment of iron status in patients with varying degrees of renal insufficiency is even less well defined. Despite the assumption by the K/DOQI of similar parameters for iron deficiency in CKD and dialysis patients,<sup>37</sup> no prospective studies have defined optimal parameters in CKD. If the development of azotemia, as postulated by some, is associated with a chronic inflammatory state and an increase in oxidative stress, then neither TSAT nor ferritin level will represent reliable indicators of iron status.<sup>40,41</sup>

#### SAFETY

It is clear that safety of the various iron preparations differs. Because of the potential for the appearance of life-threatening anaphylactoid reactions, safety of the various iron compounds naturally has focused on the relative frequencies of these reactions.<sup>21,36,42</sup> Assessment of large clinical databases suggests that the incidence of anaphylactoid reactions reported for iron dextrans is less than previously reported.<sup>8,9</sup> Evidence for immunologically based hypersensitivity is relatively sparse, and the generation of *de novo* antidextran antibodies remains an extremely in-

frequent phenomenon.<sup>43</sup> Nonetheless, both iron sucrose and iron gluconate have been associated with a markedly lower incidence of life-threatening anaphylactoid reactions.

Faich and Strobos<sup>44</sup> reported an allergy-event rate of 3.3 cases per million per year for iron gluconate versus a control rate of 8.7 cases per million per year for iron dextran. In the iron-gluconate trial of 88 HD patients by Nissenson et al<sup>23</sup> using either a high-dose (eight doses of 125 mg each) or low-dose (eight doses of 62.5 mg each) regimen of this drug, three patients were withdrawn because of drug-related adverse events, none classified as anaphylactoid. Other symptoms included nausea in four patients, emesis in three patients, rash in two patients, and reports of abdominal pain, fatigue, paresthesias, chest discomfort, and syncope. Intragroup comparisons showed no differences among adverse events between the low- and high-dose groups or between any group and the historically assigned control group. Notably, the study was inadequately powered to detect such differences, and no type I immediate hypersensitivity reactions, hospitalizations, or deaths took place.

However, more recently, iron gluconate was reported as the "primary suspect drug" in two MEDWATCH reports in which the outcome was listed as "death" in the FDA's Adverse Event Reporting System.<sup>45</sup> Such reports do not necessarily reflect a conclusion by the FDA that iron gluconate directly caused or contributed to the effect. However, the authors strongly contend that there is no requirement for IV iron administration in complex, acutely ill, and anemic patients, particularly those with infection. In these circumstances, transfusion therapy is more efficacious and expeditious. In addition, we advocate for the avoidance or discontinuance of parenteral iron therapy during active infective and/or inflammatory states.

Iron sucrose has compiled a consistent safety record after its introduction into the European market in 1950. Using data collected and analyzed from semiannual safety reports submitted to worldwide regulatory authorities that incorporate information from greater than 1,600 patients enrolled in 36 clinical trials of iron sucrose, the number of vials of iron sucrose was estimated to quantitate the number of doses and patients treated between 1992 and February 2001.<sup>46</sup> This

summary concluded that only 52 anaphylactoid reactions occurred consequent to the administration of 20 million doses of iron sucrose injection to 1,004,477 patients worldwide. Of these, 22 cases were considered serious, an incidence of 0.002%, and all patients recovered uneventfully. This type of spontaneous reporting tends to underestimate the true incidence of events, but includes safety results of all clinical trials in which iron sucrose is known to have been used. For example, the very low rate of anaphylactoid reactions recently was confirmed by a study of 61 centers in the United States in which no anaphylactoid reactions occurred after administration of 8,590 iron sucrose doses to 665 HD patients in accordance with K/DOQI guidelines for TSATs and ferritin levels.<sup>47</sup>

The use of newer iron compounds is obviously of vital importance to patients with documented iron dextran intolerance. Direct assessment of the safety profile of iron sucrose of such patients was performed by Van Wyck et al<sup>42</sup> in an open-label, single-arm, prospective study of 23 patients who had previously shown sensitivity to iron dextran. Patients were segregated into two groups according to the severity of dextran-related side effects. The mild-reaction group had experienced symptoms of urticaria, pruritus, or back pain, whereas the severe-reaction group had experienced symptoms of dyspnea, wheezing, stridor, angioedema, or hypotension. Mild-reaction group patients were administered iron sucrose as 100-mg IV push doses during 10 sequential HD sessions. The severe-reaction group was administered iron sucrose as either ten 100-mg IV injections over 5 minutes or ten 100-mg infusions of iron sucrose in 0.9% sodium chloride over 15 to 30 minutes. A total of 223 doses of iron sucrose were administered by study end. Overall, no serious drug reaction was recorded, and no individual discontinued the study because of an adverse drug reaction. Intradialytic blood pressure monitoring showed no hypotensive effects attributable to iron sucrose. Minor reactions included pruritus in 4 patients and a transient metallic taste during drug administration in 1 patient that resolved spontaneously. This symptom was deemed unlikely to be related to iron sucrose because it was present in the predosing nontreatment observation period in 3 of these individuals.

Warnock et al<sup>48</sup> conducted a similar trial with iron gluconate in iron-dextran-sensitive patients. One hundred forty-four of 2,317 patients were deemed iron-dextran allergic and administered iron gluconate in a double-blind trial in which both patients and investigators were blinded to active drug or saline placebo. Three patients (2.1%) were iron-gluconate intolerant; 2 patients manifested a pseudoallergic reaction with an elevation of serum tryptase levels to greater than 100% of baseline (indicative of mast cell degranulation), and 1 patient developed a transient life-threatening reaction. However, it is important to note that 8 of the 2,173 subjects who were iron-dextran tolerant were iron-gluconate intolerant. Thus, intolerance to iron dextran does not automatically imply tolerance to newer parenteral forms of iron, and due diligence must be maintained whenever parenteral iron of any form is administered.

Charytan et al<sup>49</sup> reviewed the multicenter experience of 66 iron-depleted patients who were intolerant to either iron dextran, iron gluconate, or both. These patients were administered a median dose of 1,000 mg of iron sucrose (range, 500 to 5,000 mg) as ten 100-mg infusions, and only a single patient developed a significant adverse drug reaction to iron sucrose that was ultimately obviated by antihistaminic premedication. The lack of iron sucrose-associated anaphylactoid reactions also was substantiated in a separate trial involving 623 patients with ESRD from 61 HD centers in which no individual required discontinuation from either the iron-correction or maintenance arms of the study because of anaphylactoid reactions.<sup>47</sup> Notably, several individuals who had previously shown intolerance to iron dextran and iron gluconate tolerated iron sucrose injection.

Nonanaphylactoid reactions represent other adverse events that may transpire during IV iron delivery. For the iron dextrans, strongly bound type I iron complexes, such adverse events have included the development of non-life-threatening hypotension, nausea, and exanthema. Nonimmunologic responses to parenteral iron most likely stem from the generation of free and highly reactive iron species, followed by the consequent production of yet more of these radicals from the dextran core.<sup>50,51</sup> This in turn can result in more release of iron from tissue ferritin

by superoxide-activated leukocytes.<sup>52</sup> The rate of generation of free radicals is critical because when a certain biotreshold is exceeded, bodily defenses that guard against oxidative stress are overwhelmed. These defenses include the compartmentalization of molecules capable of catalyzing reactions with molecular oxygen, dismutases, and glutathione peroxidases and extracellular removal of hydrogen peroxide and hydroxyl radicals by ascorbate or  $\alpha$ -tocopherol.<sup>8,10,50,53-55</sup>

The likelihood of developing transient free iron also may be influenced by the rate and route of parenteral iron administration. Notably, during the period when intramuscular iron dextran administration was in vogue, such reactions were virtually absent, possibly because of the relatively longer transfer time of reactive iron species from depot intramuscular stores to the plasma compartment. Similarly, the administration of smaller doses of iron dextran at slower rates (5 mg/min) may explain the lesser frequency of adverse reactions during maintenance iron therapy as opposed to regimens that proactively replenish iron.

Clinical implications of intermittent oxidative stress from parenteral iron therapy have not been definitively established, but may include accelerated atherogenesis<sup>56</sup> and possibly an increased risk for infection.<sup>55,57</sup> Dialysis patients have a multitude of risk factors for cardiac disease, a portion of which arise uniquely from abnormalities associated with CKD.<sup>58</sup> An important issue is that of possible risk for infection. Before the widespread use of epoetin, iron overload was common and associated with increased susceptibility to infection,<sup>59,60</sup> presumably because of impaired neutrophil function.<sup>61</sup> More recently, HD patients with greatly elevated ferritin levels ( $\geq 650$  ng/mL [ $\geq 1,461$  pmol/L]), but low serum iron levels ( $\leq 60$   $\mu$ g/dL [ $\leq 10.7$   $\mu$ mol/L]) and low TSATs ( $< 20\%$ ; functional iron deficiency), were shown by Patruta et al<sup>62</sup> to manifest polymorphonuclear leukocyte dysfunction. These uremic patients were administered only 10 to 20 mg of iron sucrose after their HD sessions, but showed impairment of phagocytosis and intracellular killing of bacteria and oxidative burst. These impairments also were observed in patients with normal renal function who had clinical evidence of iron overload from either multiple blood transfusions or hereditary hemochromatosis. There-

fore, it was concluded that leukocyte impairment stemmed from a surfeit of storage iron, and overtreatment with IV iron should be avoided.

Others have contended that hyperferritinemia to levels up to 800 to 1,000 ng/mL (1,798 to 2,247 pmol/L) have not been proven harmful,<sup>8</sup> and "infectious complications of hyperferritinemia" were not observed in the initial trials of epoetin-treated patients.<sup>63</sup> More recently, Parkkinen et al<sup>64</sup> reported the appearance of bleomycin-detectable iron (BDI), ie, potentially catalytically active iron, in sera from 7 of 12 HD patients within 3.5 hours after the administration of 100 mg of iron sucrose over 10 to 30 minutes. The appearance of BDI inhibited the normal response of patient sera to inhibit the growth of *Staphylococcus epidermidis*, a bacterium that cannot access transferrin-bound iron to facilitate its growth. Inhibitory properties of sera were restored by the addition of iron-free apotransferrin to sera, implying that its restorative properties were related to its action as an "iron sink." There are no published direct head-to-head studies comparing iron dextran, iron gluconate, and iron sucrose on the generation of BDI or their potential to facilitate infection. However, the therapeutic success of parenteral iron therapy in doses exceeding those used in these studies supports its ongoing use in clinically uninfected individuals while further data regarding the putative iron-associated potential for promoting infection are accumulated.

#### LARGE-DOSE REGIMENS OF NONDEXTRAN IRONS

More recently, trials of the nondextran-containing irons that involve greater than previously used doses have been performed. Promulgation of such regimens includes their adoption in the outpatient setting for pre-ESRD individuals and peritoneal dialysis patients, with the provisos of greater convenience and equivalent efficacy. The greater bioavailability of the nondextran irons precludes, at least to some extent, that proportion of iron rendered biounavailable after its exclusion from the developing erythron after its entrapment by the reticuloendothelial system.<sup>65</sup> Chandler et al<sup>66</sup> performed a large single-dose study to evaluate the tolerability of various doses of iron sucrose administered in normal saline as a 2-hour infusion. Three hundred eighty-five HD or continuous ambulatory peritoneal dialysis patients

or renal transplant recipients were administered 200-, 300-, 400-, or 500-mg doses of iron sucrose. No adverse events were detected among 89 patients administered a 200-mg infusion or 185 patients administered 300-mg doses. Adverse-event rates of 22% and 36% were documented in the groups administered 400- and 500-mg doses, respectively. The investigators concluded that a 300-mg dose of iron sucrose delivered over 2 hours represented the maximum dose of iron sucrose safely deliverable in that interval.

Recent data from Folkert and Michael<sup>67</sup> suggest that a 250-mg infusion of iron gluconate can be safely administered over 60 minutes. Their investigation compared adverse events between a conventionally delivered 125-mg dose of iron gluconate over 10 minutes with a 60-minute 250-mg infusion. Pruritus without rash occurred in only 1 of 142 patients administered the infusion in comparison to 1,172 patients comprising the standard-dose group in which five adverse events accrued.

Lastly, Bastani et al<sup>68</sup> administered ten 250-mg and ten 500-mg infusions of iron gluconate to 13 patients with chronic renal failure or ESRD. A 10% adverse-reaction rate was detected in the 250-mg cohort, and a 30% rate, in the 500-mg group. Adverse reactions included chills, nausea or vomiting, diarrhea, syncope, and hypotension.

The safety of a 200-mg infusion of iron sucrose over 60 minutes previously has been attested to.<sup>24</sup> Moreover, Kosch et al<sup>38</sup> delineated no difference in adverse-event rates in HD patients administered either a 250-mg dose of iron sucrose over 60 minutes or an equivalent dose of iron gluconate delivered in the same period. Chandler et al<sup>22</sup> showed that 200 mg of undiluted iron sucrose could be delivered safely through a peripheral IV site in just 2 minutes. Of 163 patients administered iron supplementation in this fashion, 4 patients reported a transient metallic taste and 1 patient developed a mild immediate reaction. One hundred fifty-eight subjects remained asymptomatic during the infusion.

In patients with ESRD, iron sucrose also is well tolerated in larger doses. This was exemplified in the trial by Nyvad et al<sup>69</sup> of HD and

peritoneal dialysis patients administered either a 50- or 200-mg maintenance dose of iron sucrose. In the study of Domrongkitchaiporn et al<sup>70</sup> involving peritoneal dialysis patients administered EPO and oral ferrous sulfate, 21 anemic subjects were administered 1 g of iron sucrose as two 500-mg infusions over 4 hours separated by 7 days. In contrast to data from Chandler et al,<sup>22</sup> some, but minimal, adverse effects were noted with this high-dose regimen. For comparative purposes, in a trial of 9 peritoneal dialysis patients, Asuncion et al<sup>71</sup> reported the efficacy and safety of iron gluconate delivered as four weekly 250-mg infusions over 90 minutes. To date, implementation of iron sucrose doses that exceed 100 mg has not received FDA approval, but current data are sufficiently compelling to warrant extension of large-dose iron sucrose trials, with the aforementioned that higher doses of hematinics represent greater efficiency of iron delivery, reduce costs, and enhance patient care.

#### SUMMARY

Iron sucrose is an efficacious and safe hematinic, based on five decades of use. Iron sucrose has been studied extensively in clinical trials and postmarketing surveillance. Its adverse-event rate is substantially less than that of dextran-containing iron preparations, and it is more bioavailable than these. The safety profile of this agent at least equals that of iron gluconate, and both products can be administered in smaller doses without a test dose. In addition, large doses of iron sucrose have been administered safely. The question of whether larger doses equal to those presently reserved only for iron dextrans are equally safe or justified remains unanswered. Presented with limited data, a single 500-mg dose of iron sucrose over 4 to 5 hours is tolerated by most patients, but we do not recommend a dose of this magnitude until further data validating its safety are available. Conversely, a single 300-mg dose of iron sucrose most likely will be tolerated safely by nearly all patients.

Certainly, the future of anemia management in patients with CKD mandates that we thoroughly examine the history of this oldest of iron compounds and the accumulating data regarding it. Whether the complete elimination of iron dextran in favor of iron sucrose or another parenteral

iron is justified by evidence-based medicine awaits the judgment of the ultimate jury: ourselves, the nephrologists caring for patients with CKD.

#### REFERENCES

- Ebert BL, Bunn HF: Regulation of the erythropoietin gene. *Blood* 94:1864-1877, 1999
- Shiose A, Kuroda J, Tsuruya K, et al: A novel superoxide-producing NAD(P)H oxidase in kidney. *J Biol Chem* 276:1417-1423, 2001
- Geiszt M, Kopp JB, Várnai P, Leto T: Identification of Renox, an NADPH oxidase in kidney. *Proc Natl Acad Sci U S A* 97:8010-8014, 2000
- Van Wyck DB: Iron management during recombinant human erythropoietin therapy. *Am J Kidney Dis* 14:9-13, 1989
- Tarng DC, Chen TW, Huang TP: Iron metabolism indices for early prediction of the response and resistance to erythropoietin therapy in maintenance hemodialysis patients. *Am J Nephrol* 15:230-237, 1995
- Kleiner MJ, Van Wyck DB, Kaupke CJ, Kirlin LF: The role of iron and other factors in patients unresponsive to erythropoietin therapy. *Semin Dial* 8:29-34, 1995
- Macdougall IC: Poor response to erythropoietin: Practical guidelines on investigation and management. *Nephrol Dial Transplant* 10:607-614, 1995
- Besarab A, Frinak SJ, Yee J: An indistinct balance: The safety and efficacy of parenteral iron therapy. *J Am Soc Nephrol* 10:2029-2043, 1999
- Fishbane S, Wagner J: Sodium ferric gluconate complex in the treatment of iron deficiency for patients on dialysis. *Am J Kidney Dis* 37:879-883, 2001
- Danielson BG, Geisser P, Schneider W: Iron Therapy. St Gallen, Switzerland, Vifor, 1996, pp 55-62
- Van Wyck DB, Anderson J, Johnson K: IV iron agents donate iron to transferring in vitro. *J Am Soc Nephrol* 417A-418A, 2001 (abstr)
- Danielson BG, Salmonson T, Derendorf H, Geisser P: Pharmacokinetics of iron(III)-hydroxide sucrose complex after a single intravenous dose in healthy volunteers. *Arzneimittelforschung* 46:615-621, 1996
- Sunder-Plassman G, Hörl WH: Comparative look at intravenous iron agents: Pharmacology, efficacy, and safety of iron dextran, iron saccharate, and ferric gluconate. *Semin Dial* 12:243-248, 1999
- Campbell BC, Lawrence JR, Sumner DJ, et al: A pharmacokinetic and clinical evaluation of iron poly (sorbitol-gluconic acid) complex. *Pharmatherapeutica* 2:475-480, 1980
- Kanakakorn K, Cavill I, Jacobs A: The metabolism of intravenously administered iron-dextran. *J Haematol* 25:637-643, 1973
- Beshara S, Lundqvist H, Sundin J, et al: Kinetic analysis of <sup>52</sup>Fe-labelled iron(III) hydroxide-sucrose complex following bolus administration using positron emission tomography. *Br J Haematol* 104:288-295, 1999
- Geisser P, Baer M, Schaub E: Structure histotoxicity relationship of parenteral iron preparations. *Arzneimittelforschung* 42:1439-1452, 1992
- Charytan C, Levin N, Al-Saloum M, et al: Efficacy and safety of iron sucrose for iron deficiency in patients with dialysis-associated anemia: North American clinical trial. *Am J Kidney Dis* 37:300-307, 2001
- Seligman PA, Schleicher RB: Comparison of methods used to measure serum iron in the presence of iron gluconate or iron dextran. *Clin Chem* 45:898-901, 1999
- Besarab A, Kaiser JW, Frinak S: A study of parenteral iron regimens in hemodialysis patients. *Am J Kidney Dis* 34:21-28, 1999
- Baillie GR, Johnson CA, Mason NA: Parenteral iron use in the management of anemia in end-stage renal disease patients. *Am J Kidney Dis* 35:1-12, 2000
- Chandler G, Orlaith E, Davis CM, Williams K, Macdougall IC: Can higher doses of IV iron be given as a bolus injection. *J Am Soc Nephrol* 12:260A, 2001 (abstr)
- Nissenson AR, Lindsay RM, Swan S, Seligman P, Strobos J: Sodium ferric gluconate complex in sucrose is safe and effective in hemodialysis patients: North American clinical trial. *Am J Kidney Dis* 33:471-482, 1999
- Iron hydroxide sucrose complex in water (Venofer®) [package insert]. Shirley, NY, American Regent Laboratories, 2001
- Sodium ferric gluconate complex in sucrose injection (Ferrelecit) [package insert]. Corona, CA, Watson Pharmaceuticals Inc, and Marina Del Ray, CA, R & D Laboratories Inc, 2001
- St Peter WL, Lambrecht LJ, Macres M: Randomized crossover study of adverse reactions and cost implications of intravenous push compared with infusion of iron dextran in hemodialysis patients. *Am J Kidney Dis* 28:523-528, 1996
- Paschen HW: Efficient anemia treatment with large intravenous iron doses. *Geburtshilfe frauenheilkunde* 9:604-616, 1999
- Weisbach V, Skoda P, Rippel R, et al: Oral or intravenous iron as an adjuvant to autologous blood donation in elective surgery: A randomized, controlled study. *Transfusion* 39:465-472, 1999
- Silverberg DS, Iaina A, Peer G, Kaplan E: Intravenous iron supplementation for the treatment of the anemia of moderate to severe chronic renal failure patients not receiving dialysis. *Am J Kidney Dis* 27:234-238, 1996
- Van Wyck DB, Stivelman JC, Ruiz J, Kurlin LF, Katz MA, Ogden DA: Iron status in patients receiving erythropoietin for dialysis associated anemia. *Kidney Int* 35:712-716, 1989
- Pascual J, Teruel JL, Liano F, Sureda A, Ortuno J: Intravenous Fe gluconate-Na for iron deficient patients on hemodialysis. *Nephron* 60:121, 1992 (letter)
- Magana L, Dhar SK, Smith EC, Martinez C: Iron absorption and utilization in maintenance hemodialysis patients: Oral and intravenous routes. *Mt Sinai J Med* 51:180-183, 1984
- Stoves J, Inglis H, Newstead CG: A randomized study of oral vs intravenous supplementation in patients with progressive renal insufficiency treated with erythropoietin. *Nephrol Dial Transplant* 16:967-974, 2001
- Silverberg DS, Blum M, Peer G, Kaplan E, Aiana A:

Intravenous ferric saccharate as an iron supplement in dialysis patients. *Nephron* 72:413-417, 1996

35. Besarab A, Amin N, Ahsan M, et al: Optimization of epoetin therapy with intravenous iron in hemodialysis patients. *J Am Soc Nephrol* 11:530-538, 2000

36. Fishbane S, Ungureanu V, Maesaka J, Kaupke CJ, Lim V, Wish J: The safety of intravenous iron dextran in hemodialysis patients. *Am J Kidney Dis* 28:529-534, 1996

37. Van Wyck DB: Lessons from NKF-DOQI: Iron management. *Semin Nephrol* 20:330-334, 2000

38. Kosch M, Bahner U, Bettger H, Matzkies F, Teschner M, Schaefer RM: A randomized controlled parallel-group trial on efficacy and safety of iron sucrose (Venofer) vs iron gluconate (Ferrolecit) in haemodialysis patients treated with rHuEpo. *Nephrol Dial Transplant* 16:1239-1244, 2001

39. Fishbane S, Shapiro W, Dutka P, Valenzuela OF, Faubert J: A randomized trial of iron deficiency testing strategies in hemodialysis patients. *Kidney Int* 60:2412-2414, 2001

40. Hasselwander O, Young IS: Oxidative stress in chronic renal failure. *Free Radic Res* 29:1-11, 1997

41. Roselaar SE, Nazhat NG, Winyard PG, Jones P, Cunningham J, Blake DR: Detection of oxidants in uremic plasma by electron spin resonance spectroscopy. *Kidney Int* 48:199-206, 1995

42. Van Wyck DB, Cavallo G, Spinowitz BS, et al: Safety and efficacy of iron sucrose in patients sensitive to iron dextran: North American clinical trial. *Am J Kidney Dis* 36:88-97, 2000

43. Fleming LW, Stewart WK, Parratt D: Dextran antibodies, complement conversion, and circulating immune complexes after intravenous iron dextran therapy in dialyzed patients. *Nephrol Dial Transplant* 7:35-39, 1992

44. Faich G, Strobos J: Sodium ferric gluconate complex in sucrose: Safer intravenous iron therapy than iron dextrans. *Am J Kidney Dis* 33:464-470, 1999

45. Food and Drug Administration: Adverse Event Reporting System (AERS); Freedom of Information (FOI) Report. Rockville, MD, Food and Drug Administration, July 9, 2001

46. Macdougall I, Bailie G, Richardson D, Tanner J, Gagnon SP: Worldwide safety profile of iron sucrose injection (Venofer®): Analysis of 1,004,477 patients from 1992 to 2001. *J Am Soc Nephrol* 12:333A, 2001 (abstr)

47. Lunde N, Pennell P, Charytan C, Hood S, Yee J: Safety of iron sucrose in the general hemodialysis population. *J Am Soc Nephrol* 12:359A-360A, 2001 (abstr)

48. Warnock DG, Coyne DW, Michael B, Strobos JT: Administration of sodium ferric gluconate complex to iron-dextran-sensitive hemodialysis patients. *J Am Soc Nephrol* 12:365A, 2001 (abstr)

49. Charytan C, Spinowitz BS, Al-Saloum M, Bheem-Reddy S, Murugan T: Iron sucrose may be safely administered to dialysis patients intolerant to other parenteral iron products. *J Am Soc Nephrol* 12:353A, 2001 (abstr)

50. McCord JM: Superoxide production and human disease, in Jesaitis A, Dratz E (eds): *Molecular Basis of Oxidative Damage by Leukocytes*. Boca Raton, FL, CRC, 1992, pp 225-239

51. Thomas CE, Morehouse LA, Aust SD: Ferritin and

superoxide-dependent lipid peroxidation. *J Biol Chem* 260:3275-3280, 1985

52. Biemond P, van Eijk HG, Swaak AG, et al: Iron mobilization from ferritin by superoxide derived from stimulated polymorphonuclear leukocytes. *J Clin Invest* 73:1576-1579, 1984

53. Cord JM: Free radicals and inflammation: Protection of synovial fluid by superoxide dismutase. *Science* 185:529-531, 1974

54. Cristol JP, Bosc JY, Badiou S, et al: Erythropoietin and oxidative stress in haemodialysis: Beneficial effects of vitamin E supplementation. *Nephrol Dial Transplant* 12:2312-2317, 1997

55. Peuchant E, Carbonneau MA, Dubourg L, et al: Lipoperoxidation in plasma and red blood cells of patients undergoing haemodialysis: Vitamins A, E, and iron status. *Free Radic Biol Med* 16:339-346, 1994

56. Corti M-C, Gaziano M, Henekens CH: Iron status and the risk of cardiovascular disease. *Ann Epidemiol* 7:62-68, 1997

57. Collins A, Ebben J, Ma J: Frequent IV iron dosing is associated with higher infectious deaths. *J Am Soc Nephrol* 8:190A, 1997 (abstr)

58. Becker RN, Himmelfarb J, Henrich WL, Hakim RM: Reassessing the cardiac risk profile in chronic hemodialysis patients: A hypothesis on the role of oxidant stress and other nontraditional cardiac risk factors. *J Am Soc Nephrol* 8:475-486, 1997

59. Boelaert JR, Daneels RF, Schurgers ML, et al: Iron overload in haemodialysis patients increases the risk for bacteremia: A prospective study. *Nephrol Dial Transplant* 5:130-134, 1990

60. Tielmans CL, Lenclud CM, Wens R, Collart FE, Dratwa M: Critical role of iron overload in the increased susceptibility of haemodialysis patients to bacterial infections. Beneficial effects of desferrioxamine. *Nephrol Dial Transplant* 4:883-887, 1989

61. Flament J, Goldman M, Waterlot Y, Dupont E, Wybran J, Vanherweghem JL: Impairment of phagocytic oxidative metabolism in hemodialysis patients with iron overload. *Clin Nephrol* 25:227-230, 1986

62. Patruta SI, Edlinger R, Sunder-Plassman G, Hörl WH: Neutrophil impairment associated with iron therapy in hemodialysis patients with functional iron deficiency. *J Am Soc Nephrol* 9:655-663, 1998

63. Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW: Correction of the anemia of end stage renal disease with recombinant human erythropoietin: Results of a combined phase I and phase II clinical trial. *N Engl J Med* 316:73-78, 1987

64. Parkkinen J, von Bonsdorff L, Peltonen S, Grönhagen-Risk C, Rosenlöf K: Catalytically active iron and bacterial growth in serum of haemodialysis patients after IV iron-saccharate administration. *Nephrol Dial Transplant* 15:1827-1834, 2000

65. Beamish MR, Davies AG, Eakins JD, Jacobs A, Trevett D: The measurement of reticuloendothelial iron release using iron-dextran. *Br J Haematol* 21:617-622, 1971

66. Chandler G, Harchowal J, Macdougall IC: Intrave-

nous iron sucrose: Establishing a safe dose. *Am J Soc Nephrol* 38:988-991, 2001

67. Folkert FW, Michael B: Safety of sodium ferric gluconate complex in higher individual doses. *J Am Soc Nephrol* 12:379A, 2001 (abstr)

68. Bastani B, Jain A, Pandurangan G: The incidence of side effects associated with high-dose ferric gluconate (Ferrlecit) in patients with severe chronic renal failure (CRF). *Am J Kidney Dis* 37:12A, 2001 (abstr)

69. Nyvad O, Danielsen H, Madsen S: Intravenous iron-

sucrose complex to reduce epoetin demand in dialysis patients. *Lancet* 344:1305-1306, 1994

70. Domrongkitchaiporn S, Jirakanont B, Atamasrikul K, Ungkanont A, Bunyaratvej A: Indices of iron status in continuous ambulatory peritoneal dialysis patients. *Am J Kidney Dis* 34:39-35, 1999

71. Asuncion MJ, Arruda JAL, Lash JP: "High dose" sodium ferric gluconate (Ferrlecit®) is safe and effective in peritoneal dialysis patients. *J Am Soc Nephrol* 12:357A, 2001 (abstr)