Structure, Chemistry, and Pharmacokinetics of Intravenous Iron Agents

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Structure and Chemistry
All intravenous (IV) iron agents are colloids that consist of spheroidal iron-carbohydrate nanoparticles. At the core of each particle is an iron-oxyhydroxide gel. The core is surrounded by a shell of carbohydrate that stabilizes the iron-oxyhydroxide, slows the release of bioactive iron, and maintains the resulting particles in colloidal suspension. IV iron agents share the same core chemistry but differ from each other by the size of the core and the identity and the density of the surrounding carbohydrate. Differences in core size and carbohydrate chemistry determine pharmacologic and biologic differences, including clearance rate after injection, iron release rate in vitro, early evidence of iron bioactivity in vivo, and maximum tolerated dose and rate of infusion.

Early experience demonstrated the hazards posed by administering inorganic ferric (Fe$^{3+}$) iron unprotected by carbohydrate. Profound toxicity limited parenteral free ferric iron administration to 8 mg (1), the approximate total iron-binding capacity of transferrin in the plasma of an adult. Formulations that present ferric iron as colloidal ferric hydroxide permitted higher doses, but common and severe hypotensive reactions precluded routine use (2). Chelating the colloidal ferric hydroxide particles with a carbohydrate proved a major advance in improving parenteral iron safety. Investigators who prepared their own saccharated ferric hydroxide administered as much as 1000 mg of iron intravenously over 15 min. Adverse reactions occurred but apparently were not severe because they responded to only "an electric blanket and a fluid ounce of brandy" (3). These reports led to the first commercially available iron-carbohydrate compounds, including iron dextrin (4), saccharated iron oxide (Proferrin; Sharp & Dohme, Inc., Philadelphia, PA) (5), iron dextran (6,7), iron sucrose (8), and ferric gluconate (9,10).

IV iron agents that currently are available in North America include only iron sucrose, ferric gluconate, and two iron dextran formulations. We focus discussion here primarily on agents in these three classes. However, multiple other parenteral iron-carbohydrate compounds for IV and intramuscular administration have been produced over the past 50 yr. Most are not currently marketed. Some of these agents differ by trade name but share identical chemistry, whereas others share the same generic name but differ chemically. Compounding the potential for confusion, published reports may reference either trade name or generic class but not both. Thus, to assist interpretation of the literature and minimize confusion, Table 1 lists IV iron agents by generic class, trade name, and current availability. The table includes packaging information because the older literature frequently cites iron doses by volume administered rather than by milligrams.

Use of low molecular weight (LMW) dextran to chelate high molecular weight ferric oxyhydroxide particles produced iron dextran. Iron dextran (Imferon; Fisons Ltd., Loughborough, Leicestershire, UK) was first available in the United States and the United Kingdom for intramuscular administration in 1955 (11) and for IV use in 1971. It was withdrawn from the world market in 1996. Early reports confirmed that iron dextran could be administered in doses as high as 2 to 3 g given intravenously over 4 to 10 min (12). More caution followed closely, when investigators found that patients who received iron dextran infusions were prone, at times fatally so, to anaphylaxis (13,14). Moreover, patients who were given high-dose iron dextran experienced severe reactions related to either total iron dose or rate of iron infusion (15). Two other forms of iron dextran remain available in the United States, one of which was introduced recently in Europe (Table 1).

Iron sucrose was first used in 1949 in Europe (8). Iron sucrose has been administered in IV push doses up to 200 mg over 2 to 5 min and in IV infusion doses up to 500 mg over 2 to 4 h. Iron sucrose is available in North America, Europe, and most countries worldwide.

To our knowledge, IV administration of ferric gluconate was first reported in 1977 (16,17). Ferric gluconate has been administered 125 mg over 10 min and up to 250 mg over 1 to 4 h. Ferric gluconate is available in the United States and several European countries.

Molecular Weight and Chemistry
As a result of differences in core size and carbohydrate chemistry, IV iron agents differ by overall molecular weight. Because molecular mass determinations depend highly on method, reported results for a single agent may differ substantially. Thus, direct comparative studies are best suited to assess relative particle sizes of IV iron agents. Two studies provide the needed information for the agents in the three generic classes considered here: iron dextran Imferon (73 kD), iron dextran INFeD (96 kD), and iron dextran Dexferrum (265 kD);
<table>
<thead>
<tr>
<th>Generic Class/Trade Name</th>
<th>Producer/Distributor</th>
<th>Packaging</th>
<th>Availability</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chondroitin sulfate iron colloid</td>
<td>Blutal</td>
<td>40 mg/10 ml</td>
<td>Japan and other Asian countries</td>
<td></td>
</tr>
<tr>
<td>Iron dextran</td>
<td>Imferon</td>
<td>100 mg/2 ml</td>
<td>Withdrawn</td>
<td>Withdrawn from US market 1990, other markets by 1996</td>
</tr>
<tr>
<td></td>
<td>INFeD</td>
<td>100 mg/2 ml</td>
<td>United States</td>
<td>Introduced in 1992</td>
</tr>
<tr>
<td></td>
<td>Cosmofer</td>
<td>100 mg/2 ml</td>
<td>Europe (5 countries)</td>
<td>Same as INFeD</td>
</tr>
<tr>
<td></td>
<td>Dexferrum</td>
<td>100 mg/2 ml</td>
<td>United States</td>
<td>Introduced in 1996</td>
</tr>
<tr>
<td></td>
<td>DexIron</td>
<td>100 mg/2 ml</td>
<td>Canada</td>
<td>See Dexferrum</td>
</tr>
<tr>
<td></td>
<td>Infufer</td>
<td>100 mg/2 ml</td>
<td>Canada</td>
<td></td>
</tr>
<tr>
<td>Ferric gluconate</td>
<td>Ferrlecit</td>
<td>62.5 mg/5 ml</td>
<td>United States, Germany, Italy, Israel, Hungary</td>
<td></td>
</tr>
<tr>
<td>Iron polymaltose</td>
<td>Maltofer</td>
<td>100 mg/2 ml</td>
<td>South America, Australia</td>
<td>Also referred to as iron dextrin</td>
</tr>
<tr>
<td></td>
<td>Iron saccharate</td>
<td>Vifor International, St. Galen, Switzerland</td>
<td>100 mg/2 ml</td>
<td>Also referred to as saccharated iron oxide</td>
</tr>
<tr>
<td>Ferrivenin</td>
<td>Laevosan, Austria</td>
<td>20 mg/ml</td>
<td>Withdrawn</td>
<td></td>
</tr>
<tr>
<td>Ferrum Vitis</td>
<td>Neopharma, Aschau im Chiemgau</td>
<td>20 mg/ml</td>
<td>Withdrawn</td>
<td></td>
</tr>
<tr>
<td>Fesin</td>
<td>Yoshitomi, Osaka, Japan</td>
<td>40 mg/2 ml</td>
<td>Japan</td>
<td></td>
</tr>
<tr>
<td>Iron sorbitol</td>
<td>Jectofer</td>
<td>Astra Zeneca, United Kingdom</td>
<td>100 mg/2 ml</td>
<td>Intramuscular use only</td>
</tr>
<tr>
<td>Iron sucrose</td>
<td>Venofer</td>
<td>100 mg/5 ml</td>
<td>68 countries</td>
<td></td>
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Table 2. Particle size, core size, and shell carbohydrate in three IV iron agents(20)*

<table>
<thead>
<tr>
<th></th>
<th>Particle</th>
<th>Core</th>
<th>Shell Carbohydrate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diameter (nm)*</td>
<td>Shape</td>
<td>Diameter (nm)</td>
</tr>
<tr>
<td>Ferric gluconate</td>
<td>3 ± 1</td>
<td>Spheroid</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>Iron sucrose</td>
<td>7 ± 4</td>
<td>Spheroid</td>
<td>3 ± 2</td>
</tr>
<tr>
<td>Iron dextran</td>
<td>30 ± 10</td>
<td>Spheroid</td>
<td>20–35 × 6d</td>
</tr>
</tbody>
</table>

* IV, intravenous.
* Mean ± SD.
* Dexferrum.
* Major × minor axes.

(18) and iron dextran Imferon (103 kD), iron sucrose (43 kD), and ferric gluconate (38 kD) (19). Together, these results establish the relative molecular weight of the currently available IV iron compounds to be as follows: iron dextran Dexferrum > iron dextran INFeD >> iron sucrose > ferric gluconate.

Imaging of iron-carbohydrate nanoparticles using atomic force microscopy distinguishes the iron-oxyhydroxide core from the carbohydrate shell and permits direct determination of core size. Atomic force microscopy imaging (20) confirms that the relative diameters of the overall iron-carbohydrate particles follow the sequence observed for overall molecular weight (iron dextran >> iron sucrose > ferric gluconate; Table 2) and further establishes that the relative diameters of the mineral cores follow the same sequence as those of the complete molecule. This has important implications for core surface area available for bioactive iron release (Labile Iron, Chapter 3).

Overall molecular weight affects two biologic characteristics of IV iron agents that are directly relevant to therapeutic use in patients: Rate of release of iron from the ferric hydroxide core and rate of clearance of agent from the plasma after IV administration. Iron release in vitro is related to total molecular weight in an inverse log-log manner; in short, the smaller the particle size, the more rapid the release of iron (19). The clinical implications of this effect are related to bioactive iron manifestations explored in detail elsewhere (Labile Iron, Chapter 3).

Pharmacokinetics and Internal Iron Disposition

After IV injection, iron-carbohydrate agents mix with plasma, then enter the reticuloendothelial system (RES) directly from the intravascular fluid compartment. Resident phagocytes of the liver, spleen, and bone marrow remove iron agent from the circulating plasma. Within phagocytes, iron is released from the iron-carbohydrate compound into an LMW iron pool. LMW iron either is incorporated by ferritin into intracellular iron stores or is released from the cell to be taken up by the extracellular iron-binding protein transferrin. Transferrin delivers iron to transferrin receptors on the surface of erythroid precursors, and the resulting internalization of the iron-transferrin-transferrin receptor complex supplies iron for hemoglobin synthesis and maturation of the red cell.

The precise cellular events by which iron-carbohydrate compounds are taken up by RES phagocytes and thereby cleared from plasma have not been elucidated. The observation that plasma clearance of iron dextran follows first-order kinetics after IV doses up to 500 mg but zero-order kinetics at higher doses suggests that the clearance mechanism is saturable (Figure 1) (21). No information is available on the pharmacokinetics of iron sucrose after doses >100 mg or ferric gluconate >125 mg (22).

The initial volume of distribution of iron sucrose (3.4 L) (23), like that of both forms of iron dextran (3.5 L or 55 ml/kg), (24) is equivalent to plasma volume. This is further evidence that early, direct donation of iron to transferrin is limited and relatively inconsequential at low iron doses. The reported initial volume of distribution of ferric gluconate (6.0 to 6.4 L) (22) is approximately twice the plasma space, a result that cannot readily be explained.

The clearance rate of IV iron agents from plasma ranges from rapid to very slow, depending on the molecular weight of the agent. In general, the lower the overall molecular weight, the more rapid the clearance of agent from plasma after an IV dose (Figure 2). It is interesting that studies that compared two iron dextran agents determined that the agent with the greater molecular weight showed the slower plasma iron clearance rate and longer half-life in plasma (data on file; American Regent, Shirley, NY). Thus, the sequence for plasma half-life follows the sequence for molecular weight: iron dextran Dexferrum > iron dextran INFeD >> iron sucrose > ferric gluconate.

If the rate of uptake of IV iron into the RES depends on molecular weight, then the rate of transfer of iron from the RES into circulating red cells seems to depend on the severity of iron deficiency, the rate of erythropoiesis, or circulating factors that influence those disorders. When the patient is profoundly iron deficient, incorporation of iron from IV iron agent into red cell precursors proceeds rapidly and is relatively complete within 2 to 4 wk (5,25). In the absence of evidence of iron deficiency, donation of iron from RES to red cells after IV iron administration is blunted (26), and in patients with cancer or inflammation, little or no erythron iron uptake may occur.
Sequestration and impaired release of both endogenous and external iron from resident macrophages of the RES defines RES blockade. The precise mechanism of RES blockade is unclear. Hepcidin, an iron-regulatory peptide, is released by hepatic parenchymal cells in response to inflammation or iron loading. Because hepcidin acts to decrease intestinal iron absorption and limit macrophage iron release, it is a likely candidate to explain features of RES blockade that characterize iron disposition in patients with chronic kidney disease (CKD), that is, impaired absorption of oral iron and a low transferrin saturation despite a high serum ferritin. No information is available, however, on the role of hepcidin in patients with CKD. Neither are results available on the effect of hepcidin on the fate and availability of intravenously injected iron. The amount of iron incorporated into circulating red cells subtracted from the dose of IV iron administered yields a semiquantitative estimate of the remaining, stainable, macrophage iron in bone marrow aspirates (21). The finding that iron-deficient patients may relapse after IV iron administration despite persistent stainable iron in marrow (5,28,29) suggests that some of the injected iron remains within cells as hemosiderin or intact, unmetabolized iron agent (30), deep forms of iron storage not readily accessible for erythropoiesis. Given the same iron loading dose, experimental animals show higher RES iron levels after iron dextran and iron polymaltose than after ferric gluconate and iron sucrose, suggesting that the rate of metabolism and utilization of IV iron may be lower for agents with higher molecular weights. Whatever the explanation, early iron utilization

Figure 1. Effect of intravenous (IV) iron dose on plasma disappearance of $^{59}$Fe-labeled iron dextran. At doses up to 500 mg, iron dextran disappearance shows first-order kinetics. At higher doses, disappearance kinetics are zero-order. Although the mechanism of clearance of iron-carbohydrate compounds is not known, these results suggest that the process can be saturated. Adapted from reference 21.

Figure 2. Molecular weight and plasma half-life of IV iron agents. Sources for molecular weights include the only available studies that compared two or more agents: Lawrence (18), Geisser et al. (19), and Kudasheva et al. (20). Sources for plasma half-life results include the following: For iron dextran Dexferrum and INFeD (data on file; American Regent), iron dextran Imferon (21), iron sucrose (25), and ferric gluconate (26). The plasma half-life of an IV iron-carbohydrate compound is directly related to its molecular weight.
for erythropoiesis may be variable and incomplete after IV iron administration in patients with dialysis-dependent CKD (31).

In short, the bulk of iron in iron-carbohydrate compounds after IV injection passes into RES cells and is either retained for later use or released from intracellular compartments to extracellular transferrin for delivery to marrow. A small fraction, however, likely bypasses the intracellular steps and donates iron directly to transferrin in plasma. Approximately 1 to 2% of the iron contained in iron dextran is available to bind directly to transferrin in vitro (21,32). Although this fraction is low compared with that observed for iron sucrose (4 to 5%) and ferric gluconate (5 to 6%) (32), it is sufficient to saturate unbound iron-binding capacity in vivo (21) after rapid IV administration of >500 mg of iron dextran.

**Clinical Implications**

**Dosing.** Differences in pharmacokinetics among IV iron agents have direct implications for determining dosing frequency, treatment duration, and laboratory testing intervals. Determining dosing frequency is important if, as in current practice, the total prescribed dose (often 1000 mg) is to be administered in divided doses. A reasonable dosing frequency for iron dextran agents, given plasma half-lives ranging from 30 to 60 h, would be every 2 to 7 d, a schedule convenient for patients who are undergoing hemodialysis (once to thrice weekly). However, ferric gluconate and iron sucrose, with 1- and 8-h half-lives, respectively, could be given as frequently as every 24 h, permitting a dosing frequency more suitable for hospitalized patients. To calculate the treatment duration in days, divide the total prescribed dose (mg) by the maximum tolerated single dose (mg), and multiply by the chosen treatment interval (days). Again, in practice, actual dosing intervals may be longer than minimal for logistical reasons, just as IV push doses, although lower than IV infusion doses, may be preferred for convenience.

**Laboratory Testing.** Because iron-carbohydrate compounds interfere with clinical laboratory determination of serum iron, it follows from pharmacokinetics that serum iron and transferrin saturation should be tested after most or all of the IV iron agent has been cleared: No earlier than 7 d after administration of a 100-mg dose of iron dextran, 2 wk after a 500-mg dose of iron dextran, and 24 to 48 h after a 125-mg dose of ferric gluconate or a 100-mg dose of iron sucrose.

**References**

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20. Kudasheva DS, Lai J, Ulman A, Cowman MK: Structure of carbohydrate-bound polynuclear iron oxyhydroxide nanopar-