

Parenteral Iron Therapy Options

Scott B. Silverstein¹ and George M. Rodgers^{2*}

¹Department of Pharmacy Services, University of Utah Health Sciences Center, Salt Lake City, Utah

²Departments of Medicine and Pathology, University of Utah Health Sciences Center, Salt Lake City, Utah

Parenteral iron therapy is occasionally necessary for patients intolerant or unresponsive to oral iron therapy, for receiving recombinant erythropoietin therapy, or for use in treating functional iron deficiency. There are now three parenteral iron products available: iron dextran, ferric gluconate, and iron sucrose. We summarize the advantages and disadvantages of each product, including risk of anaphylaxis and hypersensitivity, dosage regimens, and costs. The increased availability of multiple parenteral iron preparations should decrease the need to use red cell transfusions in patients with iron-deficiency anemia. *Am. J. Hematol.* 76:74–78, 2004. © 2004 Wiley-Liss, Inc.

Key words: iron deficiency; iron therapy

INTRODUCTION

Iron deficiency is a common problem occurring in normal people who experience excessive blood loss, as well as patients with inherited or acquired bleeding disorders. Oral iron replacement is usually adequate for most patients, but intolerance to oral iron, abnormal absorption due to surgery or gastrointestinal disease, significant bleeding, and noncompliance may make oral iron treatment in some patients inadequate. These patients will benefit from parenteral iron.

Iron dextran has been available in the United States for over 40 years, and there is significant medical experience with its efficacy and toxicity. Because fatalities and less severe allergic reactions have been associated with iron dextran-induced anaphylaxis, many clinicians are reluctant to use this product. Over the past few years, the Food and Drug Administration (FDA) has approved two new parenteral iron products for use in the United States. A comparative review of the safety of parenteral iron preparations has been reported in dialysis patients [1]. The objectives of this review are to summarize the available parenteral iron products and to compare their advantages and disadvantages.

PARENTERAL IRON PRODUCTS

Table I summarizes the three parenteral iron products. Although the two newer products (ferric gluconate and

© 2004 Wiley-Liss, Inc.

iron sucrose) have been used in Europe, the former for over 30 years and the latter for 50 years, their approval in this country occurred only within the past 4 years. The specific FDA approval for the new drugs is for iron deficiency anemia in patients with chronic renal failure and for hemodialysis patients receiving erythropoietin supplementation [2,3]. However, these products are also being used off-label to treat iron deficiency from any cause as well as “functional iron deficiency” in cancer and renal failure patients.

PHARMACOLOGY

Table II compares the pharmacological properties [4,5] of these three products. Although these properties vary amongst the iron products, the disposition of iron in the body is similar for all and is governed by the degree of iron-deficiency anemia. Following parenteral administration of iron, the iron-carbohydrate complex is separated by the reticuloendothelial system. Iron is gradually released into the circulation

*Correspondence to: Dr. George M. Rodgers, Division of Hematology, University of Utah Health Sciences Center, Salt Lake City, UT 84132. E-mail: george.rodgers@hsc.utah.edu

Received for publication 16 October 2003; Accepted 21 October 2003

Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ajh.20056

TABLE I. Parenteral Iron Preparations

Generic name	Trade names	Other names
Iron dextran injection	INFeD®, DexFerrum®	Imferon®, ^a iron dextran
Sodium ferric gluconate complex in sucrose injection	Ferrlecit®	Ferric gluconate
Iron sucrose injection	Venofer®	Iron saccharate, ferric saccharate, iron sucrose

^aNo longer marketed in the U.S.

TABLE II. Pharmacology of Parenteral Iron Products

	Iron dextran	Iron sucrose	Ferric gluconate
Bioavailability	+	++	++
<i>t</i> _{1/2} elimination (hr)	6	5–6	1
Clearance (1,000-mg dose)	10–20 mg/hr ^a	Unknown	Unknown
<i>V</i> _d (L) ^b	Not reported	7.9	6
Dialyzed	Negligible	Negligible	Negligible
Safety profile	+	++	++
Pregnancy category ^c	C	B	B

^aCleared by the reticuloendothelial system.

^b*V*_d (L), volume of distribution in liters.

^cB and C denote pregnancy risk factors established by the FDA.

where it combines with transferrin for transport to the liver, spleen, and bone marrow. Iron then binds to bone marrow receptor sites for hemoglobin synthesis. The clearance of iron from the body is dependent on the body’s need for iron, iron storage status and the demand for body metabolic processes. A small amount of iron is eliminated in the urine. The absolute reticulocyte count can increase within 7 days and hemoglobin responses occur within 1–2 weeks of iron dextran administration. Ferric gluconate and iron sucrose are more readily available for erythropoiesis than iron dextran [6]. Increases in hemoglobin are first noted after 1 week of iron sucrose administration [7].

Iron Dextran (INFeD® or DexFerrum®)

INFeD® and DexFerrum® are iron dextran products marketed in the United States. The molecular weights of INFeD® and DexFerrum® are 165,000 and 267,000 daltons, respectively. Iron dextran is a colloidal solution of ferric oxyhydroxide complexed with polymerized dextran. Intravenous iron dextran is indicated for patients with documented iron deficiency when oral replacement therapy is unsatisfactory or inadequate. One of the advantages of iron dextran is the ability to infuse the patient’s total iron requirement

in one administration (total-dose infusion). Clinicians can conveniently treat patients in a single hospital or clinic visit with this product. However, this method has been associated with a higher incidence of adverse events. Delayed reactions of hypotension, arthralgias, myalgias, malaise, abdominal pain, nausea, and vomiting have followed total dose infusion. A 25-mg test dose should be given to all new patients started on iron dextran. Patients should be monitored for adverse effects for 1 hr after a test dose. Uneventful test doses do not exclude a patient from experiencing hypersensitivity reactions with the first dose or subsequent doses. The incidence of adverse events with INFeD® and DexFerrum® are 5.4% versus 9.7%, respectively [8]. Fletes et al. [9] reported that adverse events with DexFerrum® were 8.1-fold more common than with INFeD®. It has been hypothesized that allergic reactions to iron dextran are associated with the dextran component. Patients receiving repeat doses of iron dextran with an interval of nontreatment should receive a repeat test dose.

Iron dextran may be administered intravenously by infusion. The rate of infusion should not exceed 50 mg/min. Iron dextran is the only parenteral iron product that can also be administered by the intramuscular route. However, pain on injection, staining of the skin, unpredictable delivery, and absorption of iron make the intramuscular route undesirable. The availability of newer, safer parenteral iron therapy choices further minimizes the need for the intramuscular route.

Sodium Ferric Gluconate Complex in Sucrose Injection (Ferrlecit®)

Sodium ferric gluconate complex in sucrose for injection was FDA approved in February of 1999. The molecular weight of ferric gluconate is approximately 350,000 daltons. The recommended route of administration is by intravenous injection or infusion. The rate of administration should not exceed 12.5 mg/min. When ferric gluconate was first marketed in the U.S., a standard test dose of 25 mg in 50 mL of normal saline intravenously over 60 min was recommended. This preceded the standard dose of 125 mg in 100 mL of normal saline intravenously over 60 min. Updated package labeling has omitted the recommendation for a test dose. A standard dose of 125 mg may be administered by IV injection over 10 min. The National Kidney Foundation Dialysis Outcomes Quality Initiative (NFK-K/DOQI) [10] recommends that patients with chronic kidney disease on dialysis receive 125 mg repeated in 8 doses. If the patient’s serum ferritin is less than or equal to 100 ng/mL and the transferrin saturation is less than or equal to 20%, the dose can be repeated over 8 weeks.

In a follow-up to a double-blind study and case reports evaluating adverse drug reactions to sodium ferric gluconate, iron dextran-tolerant and -sensitive patients were analyzed for drug sensitivity to ferric gluconate [8]. Results suggested that ferric gluconate could be safely administered to iron dextran-sensitive patients, but ferric gluconate intolerance was greater in iron dextran-sensitive patients than in iron dextran-tolerant patients. Case reports also demonstrate safely administering ferric gluconate following severe reactions to iron dextran [11]. Patients with multiple drug allergies may be at an increased risk of hypersensitivity reactions [12]. Doses of 250 mg of ferric gluconate intravenously over 1 hr have been reported to be safe and well tolerated [13].

Iron Sucrose Injection (Venofer®)

Iron sucrose injection was FDA approved in November of 2000. Iron sucrose is an iron hydroxide sucrose complex in water. The molecular mass of iron sucrose is 34,000–60,000 daltons. Iron sucrose is administered by intravenous injection or infusion. The recommended schedule is to administer 100 mg intravenously over 5 min, 1–3 times weekly until 1,000 mg has been administered. The rate of administration should not exceed 20 mg per minute. A test dose is also not required and is at the physician's discretion.

Chandler et al. [14] examined the optimal doses of iron sucrose and found doses of 200–300 mg intravenously over 2 hr were well tolerated and safe. Patients that received doses of 400–500 mg intravenously over 2 hr experienced hypotension, nausea, and lower back pain. In the North American Clinical Trial, patients

with documented iron dextran sensitivity were successfully treated with iron sucrose without a test dose [15].

COMPARISON OF PARENTERAL IRON PRODUCT TOXICITIES

Table III summarizes the administration guidelines for the three parenteral iron products. The parenteral use of iron dextran has been associated with significant morbidity and fatal anaphylactic reactions. The incidence of serious, life-threatening anaphylaxis with iron dextran has been reported to be 0.6–0.7% [11,16]. The incidence of serious-life threatening reactions in a phase IV, randomized, crossover, double-blind study with ferric gluconate has been reported at 0.04% [17]. On the basis of allergy-event reporting, ferric gluconate had an allergy-event reporting rate of 3.3 episodes per million doses compared to 8.7 episodes per million doses seen with iron dextran [18]. Post-marketing data submitted to regulatory agencies reported hypersensitivity rates for iron sucrose comparable to ferric gluconate at 2.6 episodes per million doses [19]. Fatal hypersensitivity reactions have not been reported with ferric gluconate or iron sucrose. Clinical trials with ferric gluconate and iron sucrose may have enrolled too few patients to detect this rare event. Adverse events to iron dextran [5], iron sucrose [2], and ferric gluconate [3] have been reported to occur up to 50%, 36%, and 35% of patients, respectively. The most common adverse events include hypotension, hypertension, bradycardia, chest pain, nausea, vomiting, diarrhea, abdominal pain, headache, fever, allergic reaction, pruritus, malaise, arthralgias, myalgias, and back pain. Table IV summarizes the anaphylaxis and hypersensitivity risks of the three parenteral iron

TABLE III. Administration Guidelines for Parenteral Iron Products*

	Iron dextran	Iron sucrose	Ferric gluconate
Concentration	50 mg/mL (2-mL vial)	20 mg/mL (5-mL vial)	12.5 mg/mL (5-mL ampule)
IV injection (maximum rate)	NTE 50 mg/min	NTE 20 mg/min	NTE 12.5 mg/min
Test dose	<i>Required</i> on first infusion	Physician discretion	Physician discretion
Test dose	25-mg IV slow IV push	25-mg IV slow push	25-mg IV slow push or 25 mg in 50 mL of NS IV over 60 min
Dosing	100 mg	100 mg	125 mg
IV injection	100 mg over 2–5 min	100 mg IV over 5 min	125 mg IV over 10 min
Maintenance dose	Daily until calculated total amount required has been reached	1–3 times week	1,000 mg over 8 dialysis sessions
Minimum cumulative dose	Based on iron replacement calculations	1,000 mg	1,000 mg
Stability	Not reported	48 hr (concentration of 0.5–2 mg/mL)	Not reported
Diluent	0.9% sodium chloride	0.9% sodium chloride	0.9% sodium chloride
Total dose infusion	Yes	No	No
Infusion	Dilute dose in 250–1,000 mL of 0.9% NS infuse over 1–6 hr	100 mL 0.9% NS IV over 15 min	125 mg in 100 mL of NS IV over 1 hr
Routes	IM (INFed) IV infusion	IV injection IV infusion	IV injection IV infusion

*Abbreviations: NTE, not to exceed; NS, normal saline.

TABLE IV. Hypersensitivity and Adverse Drug Events (ADEs) of Parenteral Iron Products

	Iron dextran	Iron sucrose	Ferric gluconate
Serious anaphylaxis hypersensitivity	0.6–0.7%	0.002% ^a	0.04%
Hypersensitivity rate	0.2–3%	0.005% ^a	0.4%
Hypersensitivity (per million doses) ^a	8.7	2.6	3.3
ADEs (%)	Up to 50	Up to 36	Up to 35

^aEvent reporting.

products. Data from adverse event reporting and post-marketing studies suggest ferric gluconate and iron sucrose are safer alternatives compared to iron dextran.

DISCUSSION

The availability of two new parenteral iron products combined with expanding uses for parenteral iron (e.g., functional iron deficiency in cancer patients) make parenteral iron therapy options a practical topic for hematology–oncology physicians. Despite widespread use in Europe for decades and frequent use in the dialysis setting in the U.S., many physicians are not familiar or comfortable with the use of these medications. Reports of anaphylactic deaths associated with iron dextran have likely contributed to the lack of use of parenteral iron.

Although iron dextran has been linked with a higher rate of adverse events, many of these reports have been based on post-marketing data collection. A recent review of a single institution’s experience suggests that there may be similar safety profiles in clinical practice, at least between iron dextran and ferric gluconate [20]. These authors found an overall adverse reaction rate with iron dextran of 20.5% versus 23% with ferric gluconate.

Drug cost may also be a consideration in choosing parenteral iron products. The average wholesale prices (per gram of elemental iron) of the three products are summarized in Table V.

TABLE V. Costs of Parenteral Iron Products

	Iron dextran		Iron sucrose	Ferric iron gluconate
	INFeD®	DexFerrum®	Venofer®	Ferrlecit®
Cost (AWP) ^a	\$37.70/vial	\$37.71/vial	\$68.80/vial	\$43.00/ampule
Cost (per gram)	\$377.04	\$377.05	\$688.00	\$688.00

^aAWP, average wholesale price, May 2003.

RECOMMENDATIONS

1. Despite the higher adverse event rate associated with iron dextran products in some (but not all) reports, most patients will tolerate iron dextran quite well. We recommend that of the two iron dextran products on the market (INFeD®, DexFerrum®) INFeD® be used due to its better safety profile. Iron dextran also has advantages of total dose infusion and lower costs. A test dose should always be used in new patients, and consideration should be given to routinely pretreating patients with diphenhydramine and acetaminophen to minimize adverse events.
2. For patients intolerant of iron dextran, ferric gluconate and iron sucrose offer safe and effective alternatives, although their costs are substantially higher and multiple infusions are necessary to totally replete iron stores with these products. Iron dextran-sensitive patients and patients with multiple allergies who will receive one of the newer products should receive the recommended test dose before therapy.
3. For ferric gluconate and iron sucrose, the package insert guidelines should be followed regarding total dose administered per infusion. Exceeding dosages or infusion rates increases the incidence of adverse events.
4. Transferrin saturation and serum ferritin measurements are useful in deciding on the frequency of repeat parenteral iron infusions except in treating “functional iron deficiency”.
5. Patients with functional iron deficiency receiving recombinant erythropoietin supplementation may require iron replacement despite normal iron indices [21]. Adequate iron replacement can enhance the response to erythropoietin and decrease erythropoietin requirements [22].
6. Appropriate use of parenteral iron will eliminate the necessity for transfusing red blood cells in most patients with iron-deficiency anemia.

REFERENCES

1. Fishbane S, Kowalski E. The comparative safety of intravenous iron dextran, iron saccharate and sodium ferric gluconate 2000; 13(6):381–384.
2. Venofer® [package insert] Shirley, NY: American Regent Laboratories, Inc.; 2000.
3. Ferrlecit® [package insert] Florham Park, NJ: Schein Pharmaceutical, Inc.; 2001.
4. Hillman RS. Hematopoietic agents: growth factors, minerals, and vitamins. In: Hardman JG, Limbird LE, editors. Goodman and Gilman’s pharmacological basis of therapeutics. 10th edition. New York: McGraw-Hill; 2001. p 1494–1502.
5. Ifudu O. Parenteral iron: pharmacology and clinical use. Nephron 1998;80:249–256.

6. Yee J, Besarab A. Iron sucrose: the oldest iron therapy becomes new. *Am J Kidney Dis* 2002;40(6):1111–1121.
7. Charytan C, Leven N, Al-Saloum M, Hafeez T, Gagnon S, Van Wyck DB. Efficacy and safety of iron sucrose for iron deficiency in patients with dialysis-associated anemia. *North American Clinical Trial. Am J Kidney Dis* 2001;37(2):300–307.
8. Coyne DW, Adkinson NF, Nissenson AR, et al. Sodium ferric gluconate complex in hemodialysis patients. II. Adverse reactions in iron dextran-sensitive and dextran-tolerant patients. *Kidney Int* 2003;63:217–224.
9. Fletes R, Lazarus JM, Gage J, Chertow M. Suspected iron dextran-related adverse events in hemodialysis patients. *Am J Kidney Dis* 2001;37(4):743–749.
10. NFK-DOQI clinical practice guidelines for the treatment of anemia of chronic renal failure. National Kidney Foundation-Dialysis Outcomes Quality Initiative. *Am J Kidney Dis* 1997;30(4):S192–S240.
11. Bastani B, Rahman S, Gellens M. Lack of reaction to ferric gluconate in hemodialysis patients with a severe reaction to iron dextran. *ASAIO J* 2002;48(4):404–406.
12. Fishbane S, Ungureanu V, Maesak JK, Kaupke CJ, Lim V, Wish J. The safety of intravenous iron dextran in hemodialysis patients. *Am J Kidney Dis* 1996;28(4):529–534.
13. Folkert VW, Michael DO, Agarwal R, et al. Chronic use of sodium ferric gluconate complex in hemodialysis patients: safety of higher-dose (≥ 250 mg) administration. *Am J Kidney Dis* 2003;41(3):651–657.
14. Chandler G, Harchowal J, Macdougall IC. Intravenous iron sucrose: establishing a safe dose. *Am J Kidney Dis* 2001;38(5):988–991.
15. 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* 2000;36(1):88–97.
16. Hamstra RD, Block MH, Schocket AL. Intravenous iron dextran in clinical medicine 1980;243(17):1726–1731.
17. Beckie M, Coyne, DW, Fishbane S. Sodium ferric gluconate complex in hemodialysis patients: adverse drug reactions compared to placebo and iron dextran. *Kidney Int* 2002;61:1830–1839.
18. Faich G, Strobos J. Sodium ferric gluconate complex in sucrose: safer intravenous iron therapy than iron dextrans 1999;33(3):464–470.
19. Macdougall I, Bailie G, Richardson D, Tanner J, Gagnon SP. Worldwide safety profile of iron sucrose injection (Venofer®): analysis of 1,044,477 patients from 1992 to 2001. *J Am Soc Nephrol* 2001;12:333A (abstract).
20. Eichbaum Q, Foran S, Dzik S. Is iron gluconate really safer than iron dextran? *Blood* 2003;101(9):3756–3757.
21. Glaspy J, Cavill I. Role of iron in optimizing responses of anemic cancer patients to erythropoietin. *Oncology* 1999;13(4):461–473.
22. Panesar A, Agarwal R. Safety and efficacy of sodium ferric gluconate complex in patients with chronic kidney disease. *Am J Kidney Dis* 2002;40(5):924–931.