PARENTERAL IRON DEXTRAN THERAPY

Vanessa J. Kumpf and Eileen G. Holland

ABSTRACT: Parenteral iron therapy is indicated in patients with iron-deficiency anemia associated with conditions that interfere with the ingestion or absorption of oral iron. Replacement doses of iron required to replenish iron stores are based on body weight and the observed hemoglobin value. Methods of administering iron dextran are reviewed, including intramuscular and intravenous injections of the undiluted drug, intravenous infusion of a diluted preparation, and as an addition to parenteral nutrition solutions. The overall incidence of adverse reactions associated with the parenteral administration of iron is low, but the potential for an anaphylactic reaction requires that an initial test dose be given followed by careful patient observation.

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IN GENERAL, CHRONIC BLOOD LOSS is the most common cause of iron deficiency and, more specifically, gastrointestinal blood loss is the most common cause of iron-deficiency anemia. Therapy for iron-deficiency anemia includes treatment of its underlying cause and restoration of normal hemoglobin concentrations and iron stores. In the acute setting blood transfusion may be indicated to promptly supply oxygen to tissues; however, the mainstay of treatment is iron replacement accomplished by the oral, intravenous, or intramuscular routes. Although the oral route is preferred, situations exist in which the parenteral route is indicated. This article will review the use of parenteral iron therapy, including guidelines for dose and administration, adverse effects, and its use in parenteral nutrition solutions.

Indications

Indications for the administration of iron via the parenteral route are limited (Table 1).[1-4] Candidates for parenteral iron therapy are those patients who have iron-deficiency anemia associated with the inability either to adequately absorb or tolerate the oral intake of iron. Noncompliance with oral iron dosage regimens may also be an indication for parenteral iron therapy.

In addition, there are less obvious conditions that warrant parenteral iron therapy. Hemodialysis, which chronically results in significant blood loss, may necessitate the use of parenteral iron therapy to restore the hemoglobin level. A high intake of antacids or other substances that bind to iron and inhibit its absorption may also warrant the use of parenteral iron.[4] Another indication for parenteral iron may be in the patient with significant blood loss who refuses blood transfusions and in whom oral iron administration is not possible.[5]

VANESSA J. KUMPF, Pharm.D., is a Clinical Pharmacist, Nutritional Support, Department of Pharmacy, Christ Hospital and Medical Center, 4440 W. 95th St., Oak Lawn, IL 60453; and **EILEEN G. HOLLAND**, Pharm.D., is a Clinical Pharmacy Resident-Fellow, Department of Family Medicine, University of Georgia and Medical College of Georgia. **Reprints:** Vanessa J. Kumpf, Pharm.D.

Product Information

Iron dextran injection is commercially available as a sterile solution of iron dextran complex containing 5% iron and 20% dextran. It contains 50 mg/mL of elemental iron, most of which is present in the ferric state. Iron dextran is a stable, clear brown solution available in 2- and 5-mL ampuls and a 10-mL multiple-dose vial. Because of its phenol content, the multiple-dose vial should only be used for intramuscular administration.[6] In the blood, iron dextran is a highly stable complex from which elemental iron is slowly released to the carrier protein, transferrin.

Intravenous vs. Intramuscular Route

Once it is decided to replace the iron stores parenterally, it must be determined whether to give the iron via the intramuscular or intravenous route. Iron dextran was originally intended for im use; however, there are several disadvantages to giving it by small, repetitive im doses. The dose that can be administered im is limited to 2 mL (100 mg) per injection. Therefore, up to 20 injections may be needed for a single course of therapy.[7] Not uncommonly, patients experience considerable discomfort secondary to the multiple injections. Multiple im injections may also be a problem in the malnourished patient with limited muscle mass. Other risks include bleeding, staining of the skin, formation of sterile abscesses, tissue necrosis or atrophy, and sarcoma formation.[7-9] The Z-track technique of im injection, in which the subcutaneous tissue over the injection site is firmly pushed aside before inserting the needle, may minimize skin staining.

In view of the numerous problems associated with im administration, the iv route is generally preferred whenever possible. Methods of iv administration include multiple slow injections of 2 mL (100 mg) of the undiluted solution or as an infusion of a diluted preparation, referred to as total dose infusion. Table 2 compares the three methods of iron dextran administration.

Total Dose Infusion

Although the use of total dose infusion (TDI) to administer iron dextran was first introduced in 1963 and is fre-

quently used in clinical practice today, it is not currently a method approved by the Food and Drug Administration for giving iron dextran. Initial reports on the use of this technique to administer iron dextran were encouraging.[10,11] However, a study published in 1965 by Clay et al. reported seven severe reactions following the iv infusion of iron dextran in 150 pregnant or postnatal patients. Severe reactions were identified as those requiring resuscitative treatment. In all seven cases the reaction occurred within minutes of starting the infusion, the women were in the third trimester of pregnancy, and all recovered from the incident with no ill effects. Although no cause to explain this unexpectedly high incidence of reactions was identified, the authors felt this form of treatment could no longer be justified.[12] Numerous letters to the editor followed the publication of the study questioning the results.[13-15] Reasons attempting to explain why the results of this study differed from the experiences of others included: (1) possible differences in technique; (2) the group of patients studied; (3) underlying folic acid deficiency which may have been present resulting in enhanced susceptibility to a reaction; and (4) the use of dextrose 5% injection as the diluent instead of NaCl 0.9%.

Subsequent studies have been conducted to support the safety and efficacy of the TDI technique of iron dextran administration.[3,7,16,17] Halpin et al. studied six children with inflammatory bowel disease and iron deficiency anemia. The children received a single dose of iron dextran 275–840 mg in 200 mL of NaCl 0.9% over two hours. All patients demonstrated a satisfactory hemoglobin response (average increase in hemoglobin was 3.5 g/dL) with no observed adverse reactions.[17]

Benito and Guerrero compared the response of a single iv infusion to multiple im injections of iron dextran in 27 malnourished children with iron-deficiency anemia. Eighteen children received a single iv infusion of iron dextran and the remaining nine received multiple im injections on a daily or every-other-day basis until the entire calculated dose was administered. Periodic follow-up studies were performed in nearly all of the children for three months. A rise in mean hemoglobin and hematocrit values was noted in each treatment group and one child in each group developed an urticarial rash. No other adverse reactions were noted.[7]

Auerbach et al. administered a TDI of iron dextran to 87 patients with anemia to better define the type and frequency of adverse reactions and to determine if the rate of infusion or premedication influenced the frequency of adverse effects. The results demonstrated that there was no difference in the frequency of adverse effects associated with an infusion at a rate of 2 mg/min compared with 6 mg/min. Premedication with aspirin, diphenhydramine, or steroids did not appear to influence the frequency.[3] The prevailing conclusion from available studies is that TDI is a safe, efficacious, and convenient method of administering iron dextran. In addition, TDI is more cost-effective than multiple injections, requiring less time to prepare and administer the drug.

Table 1. Indications for Parenteral Iron Therapy

Conditions interfering with absorption of oral iron, e.g.:
short-bowel syndrome
subtotal gastrectomy
malabsorption syndrome
chronic bowel obstruction
inflammatory bowel disease
protein calorie malnutrition
high intake of antacids
Hemodialysis
Poor compliance with oral iron regimen

Dosage and Administration

The amount of iron required to restore the hemoglobin concentration to normal and to replenish iron stores is based on body weight and the observed hemoglobin value. The dose is calculated using the following equation:[18]

$$\text{mg iron} = 0.3 \times \text{wt} \times \frac{(100 - \text{Hgb} \times 100)}{14.8}$$

where wt = weight in pounds and Hgb = observed hemoglobin level in g/dL. This equation assumes a normal mean hemoglobin of 14.8 g/dL. For children weighing less than 13.6 kg a normal mean hemoglobin of 12.0 g/dL is used in place of 14.8 in the above equation.[19]

To determine the iron replacement dose in patients actively bleeding, a different equation is used. Estimated iron requirements are based on the assumption that 1 mL of normocytic, normochromic erythrocytes contain 1 mg of

Table 2. Methods of Iron Dextran Administration

	INTERMITTENT IM	INTERMITTENT IV	TDI
Dose	not to exceed 100 mg (2 mL) per injection not to exceed 100 mg/d (manufacturer recommendations)	not to exceed 100 mg (2 mL) per injection not to exceed 100 mg/d rate: not to exceed 50 mg/min (manufacturer recommendations)	administer calculated replacement dose over 2–6 h
Diluent	administer undiluted	administer undiluted	250–1000 mL of NaCl 0.9% injection
Test dose	25 mg (0.5 mL) im observe patient for at least 1 h	25 mg (0.5 mL) iv observe patient for at least 1h	administer approximately 25 mg of diluted preparation by iv infusion over 5–10 min observe patient for at least 1h before resuming the infusion
FDA approved	yes	yes	no
Comments	inject deeply into the upper outer quadrant of the buttock to minimize skin staining: (1) use the Z-track technique (2) use a separate needle to withdraw drug from container	iron dextran injection containing phenol should not be used for iv injection	the use of dextrose 5% injection instead of NaCl 0.9% as the diluent is associated with a higher incidence of local pain and phlebitis

FDA = Food and Drug Administration; TDI = total dose infusion.

elemental iron. The dose of iron replacement secondary to blood loss is estimated using the following equation:[6]

$$\text{Iron dextran injection (mL)} = 0.02 \times \text{blood loss (mL)} \times \text{Hct}$$

where Hct = observed hematocrit expressed as a decimal fraction.

Before any patient receives these large replacement doses, it is recommended that a test dose be given to determine the patient's susceptibility to adverse reactions.[6] A 25-mg test dose may be delivered im/iv with the undiluted solution (0.5 mL) or as an iv infusion of a diluted TDI delivered over five to ten minutes. After the test dose is given, the patient should be observed closely for at least one hour. In the absence of untoward reactions, patients receiving a TDI may be given the remaining solution over the next two to six hours.[3]

Adverse Reactions

The reported incidence of adverse reactions following iron dextran administration is low. In one series of 481 iron dextran recipients, 26 percent experienced a reaction, but in only 5 percent of these (25 patients) did the reaction limit or inhibit ordinary activity.[4] It is important to note that the incidence of adverse reactions associated with the im route is similar to that with the iv route.[1,4] Complications associated with the administration of iron dextran can be classified as mild, transient reactions; more severe, systemic complications; and anaphylactic reactions.

Mild and transient reactions such as malaise, flushing, fever, myalgia, and arthralgia are the most common and generally appear within 24 hours of administration. More severe systemic reactions include headache, dizziness, hypotension, urticaria, diaphoresis, nausea, vomiting, diarrhea, delayed arthralgia, generalized pain, and lymphadenopathy. These systemic reactions appear related to the dose and rapidity of administration.[4,20] The reported overall incidence of life-threatening anaphylactic reactions, occurring primarily during test-dose administration, is 0.1–0.6 percent.[4] Thus, it is recommended that iv diphenhydramine (50 mg), epinephrine (0.3–0.5 mL of 1:1000 solution), methylprednisolone (100 mg), oxygen, and other supportive equipment be available at the patient's bedside during the test dose.[1,4] Although the incidence of anaphylactic reactions does not appear to differ significantly between the im and iv routes of iron administration, an anaphylactic reaction following an im injection may require prolonged treatment due to slow absorption from the injection site.

Depending on the route of administration, local reactions may be observed at the injection site. Phlebitis, which occurs in a small percentage of patients receiving a TDI of iron dextran, may be minimized by diluting the iron dextran in NaCl 0.9% rather than dextrose 5%.[1,2] As previously mentioned, the im administration of iron may be associated with severe pain, formation of sterile or pyogenic intramuscular abscesses, tissue staining due to residual iron and melanin deposition, sarcoma formation of the buttock, and muscle necrosis with ulceration.[8,9]

An increased susceptibility to bacterial infections has been observed in neonates receiving prophylactic iron dextran.[21] It has been suggested that excessive amounts of circulating iron may stimulate growth of bacteria in these patients. In a similar manner, an increased risk of infection may also exist for malnourished patients with low serum transferrin concentrations. When these patients are given a substantial amount of iron, an excessive level of circulating free iron may result. Therefore, a blood transfusion may be an option to consider in patients with severe protein malnutrition who require treatment for iron-deficiency anemia.[22]

Hepatosplenic siderosis, the accumulation of iron in the liver and spleen, has been observed in hemodialysis patients receiving long-term intravenous iron dextran therapy.[23] These patients may exhibit a paradoxical depletion of iron in the bone marrow and only small increases in hematocrit values. A lack of equilibrium between iron taken up by the reticuloendothelial system (primarily liver and spleen) and marrow iron may exist in these patients. The result is a lack of accessible iron for erythropoiesis. Also contributing to the risk of developing hepatosplenic siderosis with parenteral iron dextran is that this route bypasses the intestinal mechanism for the regulation of iron absorption coupled with a limited ability of the body to excrete excessive amounts of iron.[24]

Individuals with a history of allergies, asthma, or active inflammatory disease appear to be highly susceptible to the adverse effects of iron dextran. Other high-risk patients are those with active rheumatoid arthritis or active systemic lupus erythematosus. An 80–90 percent risk of developing an adverse reaction has been reported in these patient populations.[1] Therefore, extreme caution should be observed when administering iron dextran to these groups of patients and they should all receive the standard test dose. Premedication with methylprednisolone 100 mg iv is also recommended.[3]

Addition to Total Parenteral Nutrition

Total parenteral nutrition (TPN) solutions have been used as a vehicle for the administration of iron dextran in both maintenance[20,25] and therapeutic replacement doses.[2,5] Iron is not routinely added to TPN solutions and is not a component of current injectable multiple trace-element preparations. Although protein hydrolysate solution contained an amount of iron that appeared to meet daily requirements, its use has been replaced with synthetic amino acid solutions that contain only negligible amounts of iron.[26,27] Iron supplementation is not required during short-term therapy in patients without existing iron deficiency. However, the use of low-dose daily or periodic iron supplementation via TPN solutions in patients receiving long-term therapy (e.g., two to three months or longer) has become common practice to meet estimated requirements.

Norton et al. prospectively evaluated varying dosages of iron dextran (0–25 mg/d) added to TPN solutions in 42 patients requiring at least 20 days of TPN. Based on serum iron concentration response a dose of 12.5 mg/d was determined most appropriate. However, the addition of iron did not affect hemoglobin levels, reticulocyte counts, transfusion requirements, or red blood cell indices. In addition, it is unknown whether the increase in measured serum iron was transferrin-bound or iron-dextran-bound.[25] Although this study failed to document a clear benefit to the use of low-dose iron supplementation in these patients, there was no evidence of risk associated with its use. No adverse reactions were observed and the incidence of sepsis was not increased with increasing doses of iron, based on study cri-

teria. In fact, no allergic or systemic reactions have been reported to date in any patients receiving low-dose iron dextran diluted in TPN solutions.

In opposition to the routine practice of parenteral iron administration in the long-term TPN patient is a current report addressing trace-element metabolism in adults on TPN, including long-term home TPN. The report was prepared at the request of the Committee on Clinical Issues in Health and Disease of the American Society of Clinical Nutrition. It recommends limiting the administration of parenteral iron to those TPN patients with well-documented iron deficiency and established intolerance or inability to absorb oral iron.[28] The recommendation was based on the potential for the accumulation of iron in the liver and spleen and resulting organ damage, which has been observed in hemodialysis patients given parenteral iron routinely.[23] It was also based on the theoretical risk of infection associated with parenteral iron administration, as previously discussed. The report does recognize, however, the difficulty in diagnosing iron deficiency in malnourished patients on TPN therapy.

If the diagnosis of iron deficiency is determined, the use of TPN solutions as a vehicle for the administration of an iron replacement dose may be considered. The addition of repletion doses of iron to TPN solutions was clinically evaluated in eight patients with moderate-to-severe anemia who refused blood transfusions. Total doses of iron dextran ranged from 1.6 to 7 g, with a maximum concentration of 500 mg/L. In the six patients with acute blood loss, hemoglobin levels increased from a mean initial value of 5.0 g/dL (range 2.6–8.4) to a mean value of 10.6 g/dL (range 7.5–12.8). Final hemoglobin values were measured within a range of 7–21 days after completion of the iron dosage regimen. In the two patients with chronic anemia, hemoglobin levels increased from an initial mean value of 3.8 g/dL to a mean of 10.6 g/dL over a mean treatment period of 121 days. No adverse reactions were observed in any patients. The authors concluded that replacement doses of iron dextran via TPN solutions can stimulate hematopoiesis and allow rapid and safe repletion of the red blood cell mass.[5] From a compatibility and stability standpoint, the high concentration of iron dextran (500 mg/L of TPN) used in this study has not been evaluated.

No physiochemical evidence of instability or incompatibility is apparent when iron dextran is added to TPN solution (100 mg/L) and stored at room temperature for 18 hours.[29] Longer periods of storage or higher concentrations in conventional TPN solutions have not been evaluated. A single study evaluating the stability of iron dextran in a total nutrient admixture tested a concentration of 50 mg/L stored at 4 °C for 14 days. By day 14, light microscopy revealed that the lipid particles in the admixture were transformed from a normal spherical shape to an elongated shape. The authors recommend a 24-hour room temperature expiration date when iron dextran is added to a total nutrient admixture.[30]

Summary

Therapy with parenteral iron dextran is limited to patients with documented iron deficiency anemia associated with conditions which preclude the use of oral iron therapy. Currently, the only FDA-approved method of administering iron dextran is via multiple intramuscular or intravenous injections of the undiluted solution. However, in many patients it may be more advantageous to provide the calculated replacement dose either via a total dose infusion or as an addition to parenteral nutrition. Regardless of the method of administration, patients should first receive a test dose of iron dextran to determine susceptibility to an anaphylactic reaction.≏

References

1. FREED N. Intravenous iron replacement: indications and safety. *J Am Osteopath Assoc* 1982;*82*:115-8.
2. REED MD, BERTINO JS, HALPIN TC. Use of intravenous iron dextran injection in children receiving total parenteral nutrition. *Am J Dis Child* 1981; *135*:829-31.
3. AUERBACH M, WITT D, TOLER W, FIERSTEIN M, LERNER RG, BALLARD H. Clinical use of the total dose intravenous infusion of iron dextran. *J Lab Clin Med* 1988;*111*:566-70.
4. HAMSTRA RD, BLOCK MH, SCHOCKET AL. Intravenous iron dextran in clinical medicine. *JAMA* 1980;*243*:1726-31.
5. DUDRICK SJ, O'DONNELL JJ, RALEIGH DP, MATHENY RG, UNKEL SP. Rapid restoration of red blood cell mass in severely anemic surgical patients who refuse transfusion. *Arch Surg* 1985;*120*:721-7.
6. MCEVOY GK, ed. American hospital formulary service drug information 88. Bethesda, MD: American Society of Hospital Pharmacists, 1989:694-6.
7. BENITO RP, GUERRERO TC. Response to a single intravenous dose versus multiple intramuscular administration of iron-dextran complex: a comparative study. *Curr Ther Res* 1973;*15*:373-82.
8. GREENBERG G. Sarcoma after intramuscular iron injection. *Br Med J* 1976; *1*:1508-9.
9. FULLER JD, MCRORIE TI. Necrotic bilateral buttocks ulcerations occurring after multiple intramuscular iron dextran injections. *Arch Dermatol* 1988;*124*:1722-3.
10. BASU SK. Rapid administration of iron dextran in late pregnancy. *Lancet* 1963; *1*:1430.
11. LANE RS. Intravenous infusion of iron-dextran complex for iron-deficiency anemia. *Lancet* 1964; *1*:852-4.
12. CLAY B, ROSENBERG B, SAMPSON N, SAMUELS SI. Reactions to total dose intravenous infusion of iron dextran (Imferon). *Br Med J* 1965; *1*:29-31.
13. GOLDTHORP WO, SPENCER D, DAWSON DW. Reactions to intravenous iron dextran (letter). *Br Med J* 1965; *1*:316.
14. LANE RS, SCOTT JM. Reactions to intravenous iron dextran (letter). *Br Med J* 1965; *1*:449.
15. MANSON IW. Reactions to intravenous iron dextran (letter). *Br Med J* 1965; *1*:794.
16. VARDE KN. Treatment of 300 cases of iron deficiency of pregnancy by total dose infusion of iron-dextran complex. *J Obstet Gynaecol Br Commonw* 1964;*71*:919-22.
17. HALPIN TC, BERTINO JS, ROTHSTEIN FC, KURCYZNSKI EM, REED MD. Iron-deficiency anemia in childhood inflammatory bowel disease: treatment with intravenous iron-dextran. *JPEN* 1982;*6*:9-11.
18. HANSON DB, HENDELES L. Guide to total dose intravenous iron dextran. *Am J Hosp Pharm* 1974;*31*:592-5.
19. BOLINGER AM, KORMAN NR. Iron deficiency anemia. In: Young LY, Koda-Kimble MA, eds. Applied therapeutics: the clinical use of drugs. Vancouver, WA: Applied Therapeutics, 1988:1052-60.
20. PORTER KA, BLACKBURN GL, BISTRIAN BR. Safety of iron dextran in total parenteral nutrition: a case report. *J Am Coll Nutr* 1988;*7*:107-10.
21. BECROFT DMO, DIX MR, FARMER K. Intramuscular iron-dextran and susceptibility of neonates to bacterial infections. *Arch Dis Child* 1977; *52*:778-81.
22. BOTHE A, BENOTTI P, BISTRIAN BR, BLACKBURN GL. Use of iron with total parenteral nutrition (letter). *N Engl J Med* 1975;*293*:1133.
23. ALI M, FAYEMI AO, RIGOLOSI R, et al. Hemosiderosis in hemodialysis patients: an autopsy study of 50 cases. *JAMA* 1980;*244*:343-5.
24. SOLOMONS MW. Iron. In: Baumgartner TG, ed. Clinical guide to parenteral micronutrition. Melrose Park, IL: Educational Publications, Ltd., 1984:103-14.
25. NORTON JA, PETERS ML, WESLEY R, MAHER MM, BRENNAN MF. Iron supplementation of total parenteral nutrition: a prospective study. *JPEN* 1983;*7*:457-61.