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.


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).\(^4\) 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.\(^5\)

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.\(^7\)\(^8\) 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 tech-
nique 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 reac-
tions were identified as those requiring resuscitative treat-
ment. 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 identi-
fied, 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 Rea-
sons 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 stud-
ied; (3) underlying folic acid deficiency which may have
been present resulting in enhanced susceptibility to a reac-
tion; 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 ane-
mia. 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. Eight-
teen 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 dif-
fERENCE 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.8 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 multi-
ple injections, requiring less time to prepare and administer
the drug.

**Dosage and Administration**

The amount of iron required to restore the hemoglobin
collection 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:8

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

where \(\text{wt}\) = weight in pounds and \(\text{Hgb}\) = observed hemo-
globin 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.49

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>
<thead>
<tr>
<th>Table 2. Methods of Iron Dextran Administration</th>
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<tbody>
<tr>
<td><strong>Dose</strong></td>
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<tr>
<td>mg (2 mL) per injection</td>
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<tr>
<td>100 mg/d</td>
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<tr>
<td>Diluent</td>
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<tr>
<td>Test dose</td>
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<tr>
<td>FDA approved</td>
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<td>Comments</td>
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**Table 1. Indications for Parenteral Iron Therapy**

<table>
<thead>
<tr>
<th>Conditions interfering with absorption of oral iron, e.g.:</th>
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<tbody>
<tr>
<td>short-bowel syndrome</td>
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<tr>
<td>subtotal gastrectomy</td>
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<tr>
<td>malabsorption syndrome</td>
</tr>
<tr>
<td>chronic bowel obstruction</td>
</tr>
<tr>
<td>inflammatory bowel disease</td>
</tr>
<tr>
<td>protein calorie malnutrition</td>
</tr>
<tr>
<td>high intake of antacids</td>
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<tr>
<td>Hemodialysis</td>
</tr>
<tr>
<td>Poor compliance with oral iron regimen</td>
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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. 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.14 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.14 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.2

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%.13 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.5,9

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 maintenance26,25 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.28 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-
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 anaphylactic reaction.

References