Original Article

Parenteral Iron Therapy: A Single Institution's Experience Over a 5-Year Period

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Parenteral iron, iron dextran, iron gluconate, iron sucrose, adverse events.

Abstract
Many patients require parenteral iron therapy for optimal correction of anemia, including cancer patients who require erythropoietic drugs. Available parenteral iron therapy options include iron dextran, iron gluconate, and iron sucrose. The purpose of this study is to summarize our institution's experience with parenteral iron therapy over a 5-year period, with a focus on comparative safety profiles. All patients receiving parenteral iron therapy over this period were included in the analysis. Chi-squared test and Fisher's exact test were used to compare the adverse event rates of each product. A total of 121 patients received 444 infusions of parenteral iron over this period. Iron dextran was the most commonly used product (85 patients) and iron sucrose was the least used (2 patients). Iron gluconate was used by 34 patients. Overall adverse event rates per patient with iron dextran and iron gluconate were 16.5% and 5.8%, respectively (P = .024). Premedication with diphenhydramine and acetaminophen before infusions of iron dextran reduced adverse event rates per infusion from 12.3% to 4.4% (P = .054). Test doses of iron dextran were used 88% of the time for initial infusions of iron dextran. All adverse events for all parenteral iron products were mild or moderate. There were no serious adverse events and no anaphylaxis was observed. Our results suggest that, if test doses and premedications are used, iron dextran is an acceptable product to treat iron deficiency. (*JNCCN* 2005;3;791–795)

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Limitations of oral iron therapy have been previously recognized in treating functional iron deficiency associated with anemia in patients on hemodialysis who are receiving erythropoietic agents.[1] More recently, functional iron deficiency has been appreciated in cancer patients with anemia who receive erythropoietic agents.[2,3] Clinical trials in cancer patients receiving chemotherapy and erythropoietic agents have clearly shown that optimal correction of anemia in these patients requires intravenous iron.[2,3]

Clinicians have three choices when considering parenteral iron therapy: iron dextran, iron gluconate, and iron sucrose.[4] Each agent has advantages and disadvantages. For example, iron dextran has been widely used, is the least expensive, and can be given in larger doses (total dose infusion). However, significant toxicity, including anaphylactic reactions and death, have been associated with iron dextran.[4,5] For these reasons, many physicians are reluctant to use this iron product.

Iron gluconate and iron sucrose are the two other parenteral iron options. Iron gluconate appears to be safer than iron dextran,[5] but has the disadvantages of higher cost and limitations in dosage, necessitating more frequent infusions to achieve iron repletion.[4] Iron sucrose is the newest parenteral iron therapy available in the United States. The data suggest that iron sucrose may be the safest parenteral iron product,[5] but like iron gluconate, it is more expensive and requires frequent infusions.

The literature shows some controversy as to whether the newer products (iron gluconate, iron sucrose) are truly safer than iron dextran.[6] In the past, two iron dextran products have been used: InFeD® and DexFerrum®. Studies now suggest that InFeD® is a safer iron dextran

preparation than DexFerrum®,[4] yet in the past, studies comparing iron gluconate to iron dextran used infusions of both iron dextran products. When one group of investigators reported their comparative safety results of iron dextran versus iron gluconate in their institution and found the toxicities to be similar (20.5% vs. 23%, respectively),[6] and another report stated that iron sucrose should be the product of choice in patients with kidney disease,[5] we began to evaluate the use of iron products at our facility and the toxicity rates associated with them.

The objective of this report is to summarize our single institution's experience with parenteral iron products over a 5-year period. From these data, we draw conclusions about comparative safety profiles, and make recommendations on choosing parenteral iron products.

Methods

This study is a retrospective analysis of parenteral iron therapy at our institution from December 1999 until March 2005. Approval was obtained from the University of Utah Health Sciences Center Institutional Review Board. All patients who received any intravenous iron product between December 1999 and March 2005 had their pharmacy records accessed. Data collected included: iron product infused, indication for treatment, number of infusions, number of test doses given, premedications given, and adverse events.

Adverse events were classified as either minor, moderate, or severe. Minor events included pruritis, flushing, nausea, headache, and local infusion site pain. Moderate events included dyspnea, abdominal pain, chest pain, hypertension, and urticaria. Anaphylaxis and any event which required hospitalization were considered severe. Statistical differences between adverse event rates were compared using the chi-squared test and the Fisher's exact test.

Results

Patient Population

Between December 1999 and March 2005, 112 patients received a total 444 intravenous iron infusions at the Huntsman Cancer Institute Infusion Clinic. Table 1 summarizes the indications for which patients were receiving the three parenteral iron products.

Table 1 Indication for Administration of Parenteral Iron

Reason for Parental Iron	Patients, *n*
Anemia of chronic disease (cancer)	20
Heavy menstrual blood loss	19
Chronic GI blood loss	16
Gastric bypass surgery	15
Hereditary hemorrhagic telangiectasias	10
GI resection	4
Ulcerative colitis	4
Crohn's disease	3
von Willebrand disease	3
Postoperative blood loss	3
Cervical bleeding	2
Severe recurrent epistaxis	2
Renal disease	2
Other*	7

*Includes: anorexia, chronic malabsorption of iron, Waldenstrom's macroglobulinemia, thalassemia, Sjögren syndrome, and fragmentation hemolysis.

Major indications for treatment included: iron deficiency because of gastric surgery (19 patients), GI bleeding (16 patients), menorrhagia in the absence of a bleeding disorder (19 patients), functional iron deficiency of cancer (20 patients), and bleeding disorders not responsive to oral iron therapy (14 patients including von Willebrand's disease and hereditary hemorrhagic telangiectasia).

Iron Product Utilization

Our hospital formulary includes all three parenteral iron products, and physicians are free to select any of the drugs. Table 2 summarizes the use of the three parenteral iron products in our institution during the study period. Of the 112 patients, 85 received iron dextran, 34 received iron gluconate, and 2 received iron sucrose. Seven of the patients in the study received both iron dextran and iron gluconate, and 2 of the patients received iron gluconate and iron sucrose.

Test Dose

Of the 85 patients receiving iron dextran infusions, 88% (75 pts) were given a test dose before receiving their first infusion of iron dextran. Two (2.6%) of these patients experienced an adverse event with the test dose. In all, 107 test doses were administered to patients

Table 2 Utilization of Parenteral Iron Therapy Products

Product	Number of Patients	Number of Infusions
Iron dextran	85	172
Iron gluconate	34	228
Iron sucrose	2	44
Total	121	444

before receiving iron dextran infusion (62% of infusions). In the iron gluconate group, 35% of patients received a test dose before the first infusion. None of these patients experienced an adverse reaction. No patient in the iron sucrose group received a test dose.

Adverse Events

Iron Dextran: Sixteen and a half percent of patients receiving iron dextran experienced an adverse reaction (14 patients). Reactions occurred during 14 of the 172 infusions (8.1%). Eight patients (9.4%) experienced a minor reaction, and 6 patients (7%) experienced moderate reactions. No patients had reactions that were classified as severe. Minor reactions included itching, flushing, nausea, headache, infusion site pain, and hives. Moderate reactions included abdominal pain, severe itching, urticaria, shortness of breath, hypertension, and chest pain. All of the moderate reactions resolved within 1 hour of stopping the infusion. One patient returned to the clinic 2 hours after finishing the infusion complaining of itching and possible swelling, but was released after 1 hour of observation.

Iron Gluconate: Two patients (5.8%) receiving iron gluconate experienced an adverse reaction. All reactions were minor. Reactions occurred during 7 of the 228 infusions (3.1%). The reactions included nausea and swelling in the throat and leg. None of the patients receiving iron gluconate experienced a delayed reaction.

Iron Sucrose: No patients in the iron sucrose group experienced an adverse reaction. However, only 2 patients received iron sucrose therapy (total of 44 infusions).

Premedication

In order to prevent minor adverse reactions, the majority of patients at our facility receive diphenhydramine and acetaminophen before infusions of iron dextran. Patients were classified as being premedicated if they received both of these medications before their iron infusion. Patients at our facility received premedications before 52.9% of iron dextran infusions (91 infusions). In the group of patients who received premedications, the adverse event rate per infusion was 4.4% (4 events in 91 infusions). In contrast, for patients who did not receive premedication before infusions the adverse event rate per infusion was 12.3% (10 events in 81 infusions). Comparison of adverse event rates with and without premedication using the Fisher's exact test yielded a *P* value of .054.

Premedication is less common at our facility with infusions of iron gluconate. Only 36.4% of infusions were preceded by premedications (83 infusions). Four of the 7 adverse reactions occurred in a patient who had received premedication.

Adverse Events Associated with Parenteral Iron Products

Table 3 summarizes the incidence of adverse events with each of the three products. Adverse events were most common with iron dextran, while they were least common with iron sucrose, although only two patients received this product during the study.

Statistical comparison of adverse event rate per infusion in iron dextran patients without premedications (rate 12.4%) to iron gluconate patients (3.1%) showed a significant difference ($P = .0035$ by Fisher's exact test). Comparing the iron gluconate group to the iron dextran with premedications (rate 4.4%) showed the two groups were similar ($P = .52$ by Fisher's exact test).

Table 3 Association of Adverse Events with Parenteral Iron Products

	Iron Dextran (85 patients)	Iron Gluconate (34 patients)	Iron Sucrose (2 patients)
Minor	8	1	0
Moderate	6	1	0
Severe	0	0	0
All	14	2	0
With premedication	4	0	0

Discussion

The importance of functional iron deficiency as a contributing factor in the anemia of cancer and the initial reports of parenteral iron efficacy in this setting have focused attention on the clinician's parenteral iron therapy options and the relative safety profile of these drugs. Two studies have been reported in the setting of functional iron deficiency of cancer; 1 used iron dextran[2] and 1 used iron gluconate.[3] Both were effective in ameliorating anemia, and adverse event rates were 7.7% for iron dextran and 12.7% for iron gluconate. Another parenteral iron product, iron sucrose, has been recently been approved in the United States, but its utility in treating the functional iron deficiency of cancer has not been evaluated.

At our institution, we have used parenteral iron for a variety of indications, including chronic bleeding disorders unresponsive to oral iron, patients with malabsorption of oral iron, as well as patients with cancer receiving erythropoietic agents. A recent report suggesting that iron sucrose should be the parenteral iron product of choice in patients with kidney disease[5] prompted us to review our institutional experience with parenteral iron products to determine if excessive adverse events were seen with any particular product. We also wanted to determine the impact of premedication in reducing adverse events.

Over the 5-year period at our institution, iron dextran was the most widely used product. This is likely because of the larger, less frequent dosing available with this product. Iron sucrose was the least-used product. Overall adverse event rates per patient with iron dextran and iron gluconate were 16.5% and 5.8%, respectively (P = .024 using chi-squared test). Reactions occurred during 8% of the infusions of iron dextran and 3.1% of the iron gluconate infusions.

Prior studies have used premedications to help minimize reactions to iron dextran. In the Auerbach et al.[2] study, patients received methylprednisolone before their infusions of iron dextran. Our data showed that whether or not a patient had received acetaminophen and diphenhydramine before their infusion of iron dextran affected how they tolerated the infusion. Adverse reactions occurred in 4.4% of iron dextran infusions when patients were treated with premedication while they occurred in 12.3% of infusions when patients did not receive premedications (P = .054).

It should be noted that, when reviewing literature about iron dextran, all iron dextran products are not equivalent. The older iron dextran products (Dex Ferrum®, Imferon®) are high molecular weight (HMW) products with a higher incidence of adverse events. In contrast, InFed® is a low molecular weight (LMW) iron dextran with a lower incidence of adverse events. Chertow et al. reviewed the effects of HMW iron dextran products, LMW iron dextran products, and iron gluconate using data submitted to the FDA between 1998 and 2000.[7] Their data analysis found that HMW iron dextran and iron gluconate actually had odds ratios of adverse events higher than that of LMW iron dextran. This suggests that prior studies using HMW iron dextran products may not be relevant to current practice.

Our findings support data from previous studies, stating that a test dose does not need to be given before the administration of iron gluconate. However, we do recommend that a test dose be given before administration of the first dose of iron dextran. Although a test dose does not preclude a patient from having a reaction to this or subsequent infusions, it can show whether a patient will be intolerant to iron dextran and allow them to be switched to another product, possibly preventing a severe reaction.

Although our study represents a single institution's experience, we believe that certain conclusions can be drawn. Our data suggest that if patients are premedicated and have received a test dose before their initial infusion, then iron dextran is an acceptable parenteral iron product. We strongly encourage the use of test doses before a patient's initial infusion of iron dextran. We also recommend that all patients receiving iron dextran should be premedicated with acetaminophen and diphenhydramine.

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