The Safety of Intravenous Iron Dextran (Dexferrum®) During Hemodialysis in Patients with End Stage Renal Disease

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The National Kidney Foundation recently published guidelines stating that regular use of intravenous iron therapy will prevent iron deficiency and promote better erythropoiesis than oral iron therapy in patients with end stage renal disease (ESRD) who are undergoing hemodialysis. Although intravenous iron dextran has been shown to be clinically effective in maintaining iron stores in such patients, some clinicians are concerned about the incidence of adverse events associated with this mode of iron supplementation. We conducted a retrospective review of adverse events associated with the use of Dexferrum® (American Regent Laboratories, Inc., Shirley, NY) in ESRD patients at an outpatient dialysis clinic. During the 6-month study period, only 1 patient out of 62 (1.6%) experienced adverse events (hypotension, chest pain) related to treatment with Dexferrum. No patients developed anaphylactoid reactions.

In patients with end stage renal disease (ESRD) who undergo routine hemodialysis, the presence of suboptimal iron stores impedes their response to recombinant human erythropoietin (epoetin) therapy (Van Wyck, 1989). *The National Kidney Foundation – Dialysis Outcomes Quality Initiative (NKF-DOQI™) Clinical Guidelines For the Treatment of Anemia of Chronic Renal Failure*, published in 1997, state that regular intravenous (IV) administration of iron will prevent iron deficiency and, thus, promote better erythropoiesis than oral iron therapy among patients who undergo hemodialysis.

Intravenous iron dextran has been shown to improve erythropoiesis and reduce epoetin requirements in hemodialysis patients (Fishbane, Frei, & Maesaka, 1995; Fishbane & Lynn, 1995). However, some clinicians are concerned about adverse events associated with this mode of therapy. In this retrospective study, adverse reactions to the iron dextran product Dexferrum® (American Regent Laboratories, Inc., Shirley, NY) were evaluated among ESRD patients at an outpatient dialysis clinic over a 6-month period.

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Patients and Methods

The records of all 62 ESRD patients who received Dexferrum at the Merrimack Valley Dialysis Center, a hospital-based dialysis unit in Methuen, Massachusetts from August 1, 1997 to January 31, 1998 were studied. Patient characteristics are summarized in Table 1. Each patient chart was examined for demographic and clinical data and any documentation of adverse reactions that occurred during Dexferrum infusion. We noted the type of adverse reaction, the severity of the reaction, and the treatment actions taken. Each case in which a reaction occurred was evaluated to determine the probability that the reaction was caused by administration of Dexferrum.

We calculated the incidence of adverse events as a percentage of the total number of patients treated with Dexferrum. Due to the small number of adverse events, we did not analyze potential predictors of such events.

Methodology

A complete retrospective review of all dialysis run sheets and nursing progress notes of patients who received Dexferrum was conducted. Dexferrum was administered to patients according to the iron monitoring parameters recommended by NKF-DOQI in its *Clinical Practice Guidelines for the Treatment of Anemia of Chronic Renal Failure* (National Kidney Foundation, 1997).

According to our protocol, a 25 mg test dose diluted in 100 ml normal saline was administered over 30 minutes. If no reaction occurred within 1 hour, the remainder of the therapeutic dose (75 mg) diluted in 100 ml normal saline was administered over 1 hour. (The use of Dexferrum diluted in an IV solution is not in the product labeling).

Results

Of the 62 patients studied, 2 (3.2%) experienced adverse events. The first, a moderate reaction, was judged to be related to Dexferrum, while the second, a cardiac arrest, was judged not to be related. We describe each case below.

The adverse event associated with Dexferrum therapy occurred in an 84-year-old, white, male with a history of coronary artery disease. He was receiving an angiotensin-converting enzyme (ACE) inhibitor (Captopril®) and had a history of a prior course of IV iron therapy. The adverse event

Table 1
Patient Characteristics

Total medical records included in analysis	62
Mean age (range)	60.8 yrs (16-92 yrs)
Race	
Asian	–
African-American	–
Hispanic	14 (23%)
Native American	–
White	48 (77%)
History of diabetes mellitus	16 (26%)
History of 2 or more comorbid diagnoses	22 (35%)
Concurrent treatment with an ACE inhibitor	10 (16%)
History of prior course of iron dextran	53 (85%)

occurred during the second dose of a course of Dexferrum treatment (dosage = 100 mg). After initiation of the Dexferrum infusion, the patient experienced chest pain and hypotension. Review of the patient's history revealed that the reaction was likely to be related to Dexferrum. The patient usually developed hypotension, without chest pain, during the second hour of dialysis when iron was not administered. In this instance, the drop in blood pressure occurred less than 30 minutes after initiation of Dexferrum. The patient also experienced chest pain and was treated with nitroglycerin. He was not hospitalized.

A cardiac arrest that was judged to have been related to a primary cardiac ischemic event rather than to Dexferrum occurred in a 68-year-old, white, male with a history of diabetes mellitus, coronary artery disease, peripheral vascular disease, cardiomyopathy, severe left ventricular dysfunction (he had an implanted pacemaker), and a history of recent sepsis. He had no history of drug allergy. He was receiving an ACE inhibitor (Lisinopril®) and had no prior course of IV iron therapy. The adverse event occurred during the first dose of Dexferrum during the first therapeutic course. A 25 mg test dose was administered with no complications; however, approximately 25 minutes after initiation of the remaining Dexferrum dose (75 mg), the patient was noted to be hypotensive and unresponsive. He had no preceding symptoms to indicate anaphylaxis, although, on presentation to the dialysis unit that day, he felt unwell in a nonspecific way. Despite resuscitation efforts, including administration of epinephrine and solumedrol, the patient expired. In a review of the events and in light of the patient's history of severe cardiac dysfunction, it was likely that his death was not related to Dexferrum.

Overall, no patient developed anaphylactic reactions or associated reactions, such as dyspepsia, dyspnea/wheezing, headache, nausea/vomiting, skin flushing, or swelling, that were associated with Dexferrum therapy.

Discussion

In addressing adverse events associated with IV iron preparations, the NKF-DOQI cited reports documenting low incidence rates of life-threatening or serious acute reactions associated with IV iron dextran. In a prospective study of Imferon® (Fisons PLC, Cheshire, England), no longer marketed in the United States, the incidence of immediate life-threatening reactions was 0.62% (3 of 481 general patients) (Hamstra, Block, & Schocket, 1980). In a retrospective chart review of patients receiving InFed® (Schein Pharmaceutical, Inc., Floral Park, NJ), the incidence of serious adverse events was 0.7% (4 of 573 dialysis patients). Overall 27 of 573 patients (4.7%) experienced an adverse reaction to InFed (Fishbane et al., 1996).

Our 6-month retrospective study revealed that adverse events occurred in 3.2% of hemodialysis patients treated with Dexferrum. Excluding the event judged to be unrelated to iron dextran administration, only 1 patient in our series, or 1.6%, experienced an adverse reaction associated with Dexferrum.

Due to the small number of events that occurred in this series of patients treated with Dexferrum, analysis of potential predictors of adverse reactions would not have been meaningful. The study of InFed found significant predictors of adverse reactions to be a history of drug allergy (odds ratio [OR], 2.4; P=.03) and a history of multiple drug allergies (OR 5.5; P=.0004) (Fishbane et al., 1996).

Limitations of our study include its retrospective nature and the fact that our study population (77% white, 23% Hispanic) lacked a more inclusive ethnic representation. Nonetheless, our findings add to the evidence that serious reactions associated with IV iron dextran therapy, in this case Dexferrum, in ESRD patients on hemodialysis are infrequent.

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