

Use of parenteral iron products and serious anaphylactic-type reactions

Diane K. Wysowski,* Lynette Swartz, B. Vicky Borders-Hemphill,
Margie R. Goulding and Catherine Dormitzer

Controversy exists about the safety of the parenteral iron dextran products, Dexferrum and INFeD, which have been associated with rare, serious anaphylactic-type reactions. In the United States, their product labels carry boxed warnings of this adverse event; some have called for the withdrawal from marketing of the higher molecular weight Dexferrum. Between 2002 and 2007, sales of Dexferrum, INFeD, and iron gluconate Ferlecit declined 32.5%, 21%, and 4.8%, respectively, while sales of iron sucrose Venofer increased 160%. Voluntary reports submitted to the Food and Drug Administration show anaphylactic reactions and symptoms for the four parenteral iron products. Because of underreporting, possible differential reporting, absence of iron dextran brand names, and incomplete use (denominator) data, incidence rates and relative risk estimates cannot be calculated. U.S. death certificate data show that for most years from 1979 through 2006, no more than 3 deaths per year were coded to “adverse events in therapeutic use of iron preparations;” brand names were not consistently recorded. Emergency department data show small numbers of visits for treatment of allergic reactions with intravenous iron preparations. The data presented herein show that allergic reactions are possible with all four parenteral iron products, and it is difficult to determine which product has the largest risk based on sales data, voluntarily submitted adverse event reports, death certificates, ED visits, and observational studies performed to date. To help differentiate risk among the parenteral iron products, the brand name of the product always should be provided on medical records, death certificates, and adverse drug reaction reports. Am. J. Hematol. 00:000–000, 2010. Published 2010 Wiley-Liss, Inc.[†]

Introduction

During the period 1992 through mid-2009, four parenteral iron products were approved by the Food and Drug Administration (FDA) for marketing in the U.S. including:

- Dexferrum (iron dextran intravenous injection, American Regent Laboratories, Inc., Shirley, NY, launched 1996, molecular weight of 265 kD [1], indicated for treatment of patients with documented iron deficiency in whom oral administration is unsatisfactory or impossible;
- INFeD (iron dextran intramuscular and intravenous injection, Watson Pharmaceuticals, Inc., Morristown, NJ, launched as INFeD in 1992 but originally launched in 1974 under a different name/manufacturer, molecular weight of 96 kD [1]), indicated for treatment of patients with documented iron deficiency in whom oral administration is unsatisfactory or impossible;
- Ferlecit (sodium iron gluconate complex or iron gluconate intravenous injection, Watson Pharmaceuticals, Inc., launched 1999, molecular weight of 38 kD [1]) indicated for treatment of iron deficiency anemia in adult and pediatric patients six years and older undergoing chronic hemodialysis and receiving supplemental epoetin therapy; and
- Venofer (iron sucrose intravenous injection, American Regent Laboratories, launched 2000, molecular weight of 43 kD [1]) indicated for chronic kidney disease patients who are non-dialysis dependent not receiving an erythropoietin, or non-dialysis-, hemodialysis-, and peritoneal dialysis-dependent patients receiving an erythropoietin.

Another iron dextran, Imferon (Fisons Ltd. Pharmaceutical Division, Loughborough Leicestershire, UK, molecular weight of 103 kD), used beginning in 1955 for intramuscular injection and for intravenous use in 1971 that carried a boxed warning for “fatal anaphylactic-type reactions,” was withdrawn from the U.S. market about 1990 and other markets by 1996

[1]. In addition, generic iron dextran injection (LyphoMed, Inc.) for intramuscular use was withdrawn from the market in 1986. Other iron dextran injectables have been marketed off and on under various names (e.g., Proferdex) and manufacturers. In the United States, iron is currently used primarily for the treatment of anemia associated with hemodialysis and is administered intravenously in that setting.

Ferumoxitol (Feraheme) intravenous injection was approved by the FDA in June, 2009; data on this drug are not included in this article.

In the United States, the product labels for the iron dextrans, Dexferrum and INFeD, carry boxed warnings for anaphylactic-type reactions. At least two studies [2,3] have implicated the higher molecular weight iron dextran, Dexferrum, with substantially higher frequencies of life-threatening adverse drug events including anaphylactic-type reactions than the lower molecular weight iron dextran, INFeD. An editorial published in 2008 [4] stated, “We urgently recommend avoiding use of HMW iron dextran in all clinical practice settings. We also recommend that the FDA withdraw this formulation of intravenous iron.”

In this article, we present data compiled by the FDA on the use of parenteral iron products in the U.S. and on the occurrence within several databases of serious anaphylac-

Office of Surveillance and Epidemiology, Food and Drug Administration, Silver Spring, Maryland

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*Correspondence to: Diane K. Wysowski, Ph.D., Division of Epidemiology, Food and Drug Administration, 10903 New Hampshire Ave., Building 22, Room 2406. Silver Spring, MD 20993. E-mail: diane.wysowski@fda.hhs.gov

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tic-type reactions with Dexferrum, INFeD, Ferrlecit, and Venofer.

Methods

We accessed several sources to obtain information on the use of parenteral iron products and anaphylactic-type reactions including the IMS Health database, the FDA's Adverse Event Reporting System (AERS) database, death certificate data, and emergency department visit databases.

Estimates of use of parenteral iron products in the U.S. were obtained from the National Sales Perspective™ database [5] of IMS Health, a pharmaceutical marketing research company. The data are based on sales data for products moving from manufacturers into various outlets within the retail pharmacy setting and non-retail markets. Outlets within the non-retail market include clinics, non-Federal hospitals, Federal facilities, HMOs, long-term care facilities, home health care, and miscellaneous channels (prisons, universities, other). Sample data are projected nationally. Each iron product's volume is expressed as the number of eaches (defined as subunits within shipping packages such as vials or syringes, a measure appropriate for injectable products) distributed to health care facilities in the United States from 2002 through 2007.

We obtained adverse event data for each intravenous iron product from the FDA's Adverse Event Reporting System (AERS) database that includes voluntarily submitted reports of adverse events suspected of being caused by drugs [6]. Numbers of reports of serious outcomes (death, hospitalization, life threatening, disability, congenital anomaly, and intervention required) and the top ranking adverse events reported for each of the four intravenous iron products were obtained. We did not review individual reports to remove duplicates or perform a manual review to match initial and follow-up reports for the same individuals, so only crude counts are provided; however, reports were unduplicated to the extent possible by computer identification. Although in most reports a close temporal relationship existed between the adverse events and drug administration, a definite causal relationship for all reports cannot necessarily be inferred. A number of reports were listed as "iron dextran" without a brand name. In an attempt to differentiate the reports for Dexferrum, INFeD, and previously marketed iron dextran products and intravenous and intramuscular routes, we used the most recent manufacturer names (Luitpold and American Regent for Dexferrum, and Schein and Watson for INFeD) and attempted to exclude reports noting intramuscular route of administration.

We obtained the annual number of U.S. deaths in which iron preparations in therapeutic use were attributed by certifiers as the underlying cause of death or as total mentions (the combination of immediate, contributing, or underlying causes, and significant conditions contributing to death) on death certificates [7] for the period 1979 through 2006, the latest year with data currently available. The data were obtained from the Division of Vital Statistics of the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, and from an NCHS website. Annual mortality data were obtained for iron preparations as a cause of death by identifying the appropriate International Classification of Diseases (ICD) codes and by obtaining the numbers of deaths associated with these codes. For 1979 through 1998, the relevant ICD ninth revision (ICD-9) code was E934.0, "adverse effect in therapeutic use of iron and its compounds" [8] and the relevant tenth revision code (ICD-10) for 1999 through 2006 was Y44.0, "adverse effect in therapeutic use of iron preparations and other antihypochromic anemia preparations" [9]. Names of individual iron products are not available from these data. Rates of total mentions per million eaches were calculated for 2002 through 2006, the years with both mortality and use data available.

The FDA in collaboration with the U.S. Consumer Product Safety Commission (CPSC) conducted a pilot study in 2002–2003 to collect and analyze death certificates for deaths attributed to drugs used therapeutically. As an extension of its ongoing surveillance activities, the CPSC collected death certificates from state health departments for the year 1999 with any of four ICD-10 codes listed as causes of death [10]. A code selected and considered relevant to iron safety was T88.7, "Unspecified adverse (allergic, hypersensitivity, idiosyncratic) effect of drug." Results from this study relevant to iron therapy are reported herein.

We accessed the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) database to identify emergency department (ED) visits made to U.S. hospitals from 2004 through 2008 for adverse drug events for any of the intravenous iron products [11] because patients experiencing serious anaphy-

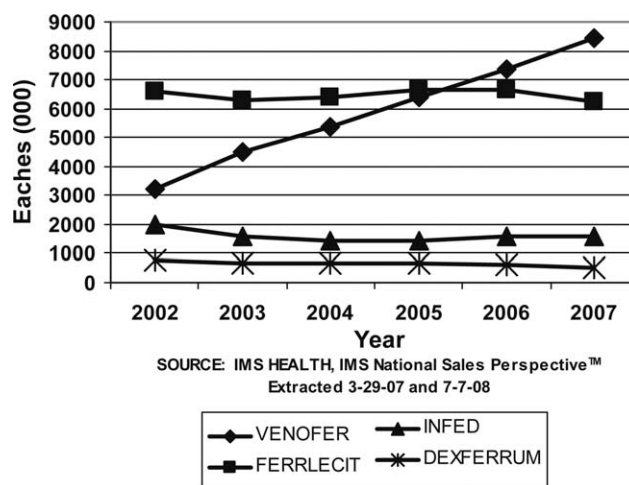


Figure 1. Projected Number of Total Eaches (in thousands) of Parenteral Iron Products Purchased by Retail and Non-Retail Channels in the United States, 2002–2007.

lactic-type reactions in a clinic setting are sometimes transferred to and treated in hospital EDs. NEISS-CADES, a joint ongoing surveillance effort of the Centers for Disease Control and Prevention, the CPSC, and the FDA, obtains data from 63 hospitals which represent a size-stratified probability sample of U.S. hospitals with a minimum of six beds and a 24-h ED [11].

We also accessed the Drug Abuse Warning Network (DAWN) *Live!* database for the period 2004–2008 to obtain the unweighted number and characteristics of ED visits associated with intravenous iron products in participating hospitals. Under the auspices of the Substance Abuse and Mental Health Services Administration (SAMHSA), DAWN monitors all drug-related visits in a nationally representative sample of non-Federal, short-stay, general hospitals that operate a 24-h ED [12]. Approximately 250 EDs participate in DAWN.

Results

Parenteral Iron Use Data

Figure 1 presents the U.S. sales data for the four parenteral iron products for 2002 through 2007. Sales are expressed in eaches (single items) contained in a unit or shipping package and purchased by providers and pharmacies. The projected number of eaches of parenteral iron sold in the U.S. increased from about 12.6 million in 2002 to over 16.8 million in 2007, a 33.5% increase. Sales increased 161% for Venofer, and declined 32.5% for Dexferrum, 21% for INFeD, and 4.8% for Ferrlecit [5].

In 2007, Venofer accounted for 50.2% of eaches of intravenous iron drug products sold in the U.S., while Ferrlecit accounted for 37.2%, INFeD, 9.5%, and Dexferrum, 3.2%. In 2007, the majority of sales of INFeD, Ferrlecit, and Venofer was to clinics, while the majority of sales of Dexferrum was to non-Federal hospitals [5].

The number of individual patients treated by each drug is not available, but Dexferrum and INFeD are reported to be capable of replacing a patient's total iron requirement in one infusion in a sitting [10], whereas Ferrlecit and Venofer are reported to require multiple infusions over several sittings. The average wholesale price per vial from 2003 through 2007 was around \$19 for Dexferrum (elemental iron 50 mg/mL), \$23 for INFeD (elemental iron 50 mg/mL), \$24 for Ferrlecit (elemental iron 12.5 mg/mL), and \$39 for Venofer (elemental iron 20 mg/mL) [5,13].

FDA's voluntarily submitted adverse drug event data

Table 1 presents a summary of FDA's adverse event reports by serious outcome for intravenous iron products from each one's initial marketing to mid-April 2007.

TABLE I. Number of U.S. Cases^a of Adverse Events Entered in AERS for Selected Parenteral Iron Products, and Types of Outcomes, from Each Product's Marketing to Mid-April, 2007

Drug	Cases	Serious	Death	Hospitalized	LT ^b	Interv ^c
Dexferrum ^e	698	524	24	160	157	214
INFeD ^f	612	478	43	188	152	90
Iron dextran ^d	124	94	7	42	42	32
Ferrlecit ^g	322	222	11	125	53	72
Venofer ^h	79	64	2	40	8	14

Source: FDA's Adverse Event Reporting System (AERS).

^a Crude counts of cases (reports entered in AERS with duplicates removed if identified by computer).

^b Life threatening.

^c Required intervention.

^d Iron dextran cases may refer to Dexferrum, INFeD, or previously marketed iron dextrans (e.g., Imferon, Proferdex, etc.).

^e Marketed from 1996.

^f Marketed from 1992; originally launched in 1974 under a different name and manufacturer.

^g Marketed from 1999.

^h Marketed from 2000.

TABLE II. Top Five Ranking Adverse Events in AERS for Parenteral Intravenous Iron Products in the U.S., From Each Product's Marketing to Mid-April, 2007

	Dexferrum	INFeD	Ferrlecit	Venofer ^a
Dyspnea	✓	✓	✓	
Back pain	✓			
Chest pain	✓	✓	✓	
Pruritus	✓			
Hypotension	✓	✓	✓	
Nausea		✓	✓	✓
Vomiting		✓	✓	✓
Infusion-related reaction				✓
Peripheral edema				✓
Dizziness				✓

Source: FDA's Adverse Event Reporting System (AERS).

^a Updated data for Venofer (through July, 2009) show that dyspnea and hypotension overtook dizziness and vomiting for the top five adverse events.

Depending on the outcome categories, Dexferrum or INFeD outnumbers the other. The top five adverse events entered in AERS for each of the four intravenous iron products are presented in Table II. Many events among the top ranked are likely indicative of an anaphylactic/hypersensitivity reaction including dyspnea, hypotension, pruritus, infusion related reaction, and others. INFeD had the largest number of reports of "anaphylactic reaction" followed by Dexferrum, Ferrlecit, and Venofer. Because of underreporting, possible differential product reporting, lack of iron dextran brand names, and incomplete use (denominator) data, incidence rates and relative risk estimates cannot be calculated.

U.S. death certificate data

Death certificate data for iron preparations are presented in Table III. Of note is that while the intravenous iron market vastly expanded during the period 2002 through 2007, the number of deaths attributed to adverse effects in therapeutic use of iron preparations was fairly constant from 1979 through 2006, and with the exceptions of 1998, 1999, 2000, and 2002, total mentions of deaths did not exceed three deaths per year. In 2002 through 2006, the mortality rate (based on total mentions of deaths for ICD-10 code Y44.0 per million eaches) for iron preparations ranged from 0.06 to 0.32 deaths per million eaches sold.

The CPSC collected 214 death certificates for year 1999 that listed the ICD-10 code T88.7, "Unspecified adverse (allergic, hypersensitivity, idiosyncratic) effect of drug," as the underlying cause of death or other cause (immediate, con-

TABLE III. Number of Deaths of the U.S. Resident Population Attributed to Adverse Effects in Therapeutic Use of Iron Preparations by Underlying Cause and Total Mentions on U.S. Death Certificates, 1979-2006

Year	Underlying cause	Total mentions ^a
1979	0	0
1980	1	1
1981	0	1
1982	0	0
1983	0	3
1984	0	1
1985	1	2
1986	0	1
1987	0	0
1988	0	2
1989	0	0
1990	0	0
1991	0	3
1992	0	3
1993	1	2
1994	0	2
1995	2	2
1996	0	1
1997	1	2
1998	2	8
1999	2	5
2000	0	4
2001	0	0
2002	0	4
2003	1	2
2004	0	1
2005	0	2
2006	1	1

Source: Public use data tape documentation. Multiple Cause of Death for ICD code E934.0 (ICD-9, 1979-1998) and ICD code Y44.0 (ICD-10, 1999-2006).

Unpublished output from the Multiple Cause of Death public use file, 2006. U.S. Dept. Health and Human Services, Public Health Service, National Center for Health Statistics, Hyattsville, MD, annual reports for 1979-2006.

^a Total mentions of the ICD code include the combination of immediate, contributing, or underlying causes, and significant conditions contributing to death.

tributing to underlying, and other significant contributing conditions). In 73 (34%) of the 214 deaths, no name other than "drug" or the ICD-10 code, T88.7, was specified [10]. For those with drug names specified, only one death was attributed to "iron dextran," but the certificate did not specify the brand name of the product [10]. On the basis of available death certificate data, iron preparations appear to be rarely attributed as the immediate, underlying, or contributing cause of death on U.S. death certificates.

Emergency department data

For the period 2004 through 2008, sample data from NEISS-CADES identified 18 emergency department (ED) visits for treatment of allergic reactions related to intravenous iron infusions. (These are counts; the number was too small to make reliable national estimates.) The reactions included a variety of symptoms (e.g., shortness of breath, chest tightness, pruritus, edema, hypotension, hives, etc.). INFeD ($n = 1$) and Venofer ($n = 1$) were the only intravenous iron drugs specifically identified. Ages of patients ranged from 20 to 57 years (median = 43 years); 16 patients were female. Four patients were admitted, one left against medical advice, and the rest were treated and released.

For the period 2004 through 2008, DAWN Live! identified a count of 27 ED visits (26 involving adverse reactions) with iron sucrose. Twenty-five visits involved female patients. Ages ranged from one person in the 18-20 year group to five in the ≥ 65 year group. Twenty-three involved patients who were treated and released, 3, admitted, and one, transferred. In addition, DAWN identified 17 ED visits (all adverse reactions) involving iron dextran. Twelve involved female patients. Ages ranged from one patient in the age group ≤ 5 years to 5 in the ≥ 65 year group. Four-

teen patients were treated and released and three were admitted. No reports of death for the parenteral iron products were reported to DAWN in 2003 through 2007 from participating medical examiners/coroners (Personal communication: Elizabeth Crane, Ph.D., M.P.H., SAMSHA).

Discussion

The data presented herein indicate that from 2002 through 2007, sales of parenteral iron preparations increased in the United States, accounted for by large sales increases for the iron sucrose Venofer, considerable sales declines for the iron dextrans Dexferrum and INFeD, and a small sales decline for the iron gluconate Ferrlecit. The decline in sales of the iron dextrans may be due to their risk of anaphylactic-type reactions and the availability of newer iron preparations with apparently lower risk.

At least two studies [2,3] have implicated the higher molecular weight iron dextran, Dexferrum, with substantially higher incidence of anaphylactic-type reactions than the lower molecular weight iron dextran, INFeD, and an editorial [4] requested that FDA remove Dexferrum from the market. However, these studies used as evidence voluntarily submitted reports of adverse drug events entered in the FDA's database. Reports of adverse drug events cannot provide incidence rates for comparisons among drugs because they are subject to underreporting and possible differential reporting, and complete use (denominator) data are not available. Furthermore, it's difficult to differentiate the iron dextrans because trade names were not provided for some reports, and trade names and manufacturers of these products, which were first launched in the 1970s, changed over time. To obtain reporting rates of an adverse event such as anaphylaxis for each product, we normally would use the number of unduplicated reports per sales data (or some other indicator of exposure). However, sales data going back as far as 1992 and 1996, the beginning of trade name INFeD and intravenous Dexferrum marketing, respectively, are not available online to the FDA. It is possible to limit reports to the period of online sales data (i.e., 2002 to year to date), but this may not be a fair analysis since reporting of adverse events declines with marketing time; therefore, older drugs with fewer recent reports may have an unfair advantage. Also, determining the true number of AERS reports of anaphylactic-type reaction is not straightforward since symptoms such as hypotension, dyspnea, cardiac disorders, etc. may be indicative of an anaphylactic reaction but not designated as such, and because changes in adverse event coding has occurred over time.

Death certificate data are not ideal for determining mortality rates associated with specific iron preparations. Doctors may not attribute an iron preparation as a cause of death or write the iron product's trade name on the certificate. Nevertheless, attribution of death should be accurate for immediate anaphylactic-type reactions, so death certificates would seem a reasonable source of data. However, aside from the ICD-code for "adverse effects in therapeutic use of iron products," there is no specific code for iron products, and unless copies (or "literals") of causes of death on certificates are obtained for a potentially relevant code, one is not able to ascertain the number of deaths attributed to iron preparations. Furthermore, complete use (denominator) data for each iron product are unavailable. Despite these shortcomings, the death certificate data do not indicate a large number of deaths due to intravenous iron products in the U.S.

The five-year NEISS-CADES and the five-year DAWN sample data also do not show many ED visits for treatment of allergic reactions related to the use of intravenous iron products. ED data do not include patients treated for ana-

phylactic-type symptoms in outpatient clinics. Like the death certificate information, these data are limited by incomplete or absent brand names and a bias toward identifying intravenous iron products administered in clinic settings (i.e., INFeD, Ferrlecit, and Venofer) rather than in hospital settings (i.e., Dexferrum).

Studies have found that Dexferrum compared with INFeD had higher frequencies of anaphylactic-type reactions [14,15], while another found similar or higher frequencies with INFeD [16]. In two large multicenter studies, the overall adverse reaction rates were low and ranged from 2/1,000,000 iron dextran doses [15] to 3.2/10,000 iron dextran exposures [16]; in one, 7 patients of 1,000,000 doses (7 of 20,213 iron dextran naïve patients) of iron dextran administered required resuscitative intravenous medicine [16]. Several studies were based on retrospective chart review that relied on staff's recording of the adverse event and the scrutiny of the researcher to find it. One study found that patients who took ACE inhibitors were at highest risk of life-threatening anaphylaxis to iron dextran (either INFeD or Dexferrum) [16], but information on drugs besides the iron preparations and other possible risk factors were not collected in most studies. This is an important omission since studies have found that history of drug allergy and multiple drug allergy were predictors of reactions [17,18] and sensitivity to iron dextran was a predictor of future reactions to other iron products [19,20]. In a multicenter, crossover, randomized double-blind, placebo-controlled trial of sodium ferric gluconate complex (Ferrlecit), 3 (2.1%) of 143 iron dextran sensitive patients exposed to Ferrlecit had suspected allergic reactions including one patient (0.7%) with a serious reaction [19]. By contrast, five patients (0.2%) among 2,194 iron dextran tolerant patients exposed to Ferrlecit had suspected allergic reactions and none had serious events.

Despite study shortcomings and lack of definitive randomized trials, the iron sucrose Venofer and the iron gluconate Ferrlecit are believed to have lower risks of serious anaphylactic-type reactions than the iron dextrans [20–27] possibly because they do not initiate an anti-dextran response [25]. A stated advantage of iron dextran, besides lower cost, is the ability to infuse a patient's total iron requirement in one administration (total dose infusion) [28–30] so clinicians can conveniently treat patients in a single hospital or clinic visit. However, the total dose infusion of iron dextran, although widely used, is an off-label method of administration [30] and it is not known if studies with adequately large sample sizes have been done to determine its relative safety.

The data presented herein show that allergic reactions are possible with all four parenteral iron products, and it is difficult to determine which product has the largest risk based on sales data, voluntarily submitted adverse event reports, death certificates, ED visits, and observational studies performed to date. Long-term safety studies have not been done [31]. To help differentiate risk among the parenteral iron products, the brand name of the product always should be provided on medical records, death certificates, and adverse drug reaction reports (submitted via <http://www.fda.gov/medwatch> or 1-800-FDA-1088).

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