Original Investigation

Comparative Risk of Anaphylactic Reactions Associated With Intravenous Iron Products

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IMPORTANCE All intravenous (IV) iron products are associated with anaphylaxis, but the comparative safety of each product has not been well established.

OBJECTIVE To compare the risk of anaphylaxis among marketed IV iron products.

DESIGN, SETTING, AND PARTICIPANTS Retrospective new user cohort study of IV iron recipients (n = 688 183) enrolled in the US fee-for-service Medicare program from January 2003 to December 2013. Analyses involving ferumoxytol were limited to the period January 2010 to December 2013.

EXPOSURES Administrations of IV iron dextran, gluconate, sucrose, or ferumoxytol as reported in outpatient Medicare claims data.

MAIN OUTCOMES AND MEASURES Anaphylaxis was identified using a prespecified and validated algorithm defined with standard diagnosis and procedure codes and applied to both inpatient and outpatient Medicare claims. The absolute and relative risks of anaphylaxis were estimated, adjusting for imbalances among treatment groups.

RESULTS A total of 274 anaphylaxis cases were identified at first exposure, with an additional 170 incident anaphylaxis cases identified during subsequent IV iron administrations. The risk for anaphylaxis at first exposure was 68 per 100 000 persons for iron dextran (95% CI, 57.8-78.7 per 100 000) and 24 per 100 000 persons for all nondextran IV iron products combined (iron sucrose, gluconate, and ferumoxytol) (95% CI, 20.0-29.5 per 100 000) , with an adjusted odds ratio (OR) of 2.6 (95% CI, 2.0-3.3; $P < .001$). At first exposure, when compared with iron sucrose, the adjusted OR of anaphylaxis for iron dextran was 3.6 (95% CI, 2.4-5.4); for iron gluconate, 2.0 (95% CI 1.2, 3.5); and for ferumoxytol, 2.2 (95% CI, 1.1-4.3). The estimated cumulative anaphylaxis risk following total iron repletion of 1000 mg administered within a 12-week period was highest with iron dextran (82 per 100 000 persons, 95% CI, 70.5- 93.1) and lowest with iron sucrose (21 per 100 000 persons, 95% CI, 15.3- 26.4).

CONCLUSIONS AND RELEVANCE Among patients in the US Medicare nondialysis population with first exposure to IV iron, the risk of anaphylaxis was highest for iron dextran and lowest for iron sucrose.

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In 2010, anemia affected one third of the global population, and iron deficiency was the most common cause.[1] A model using data throughout 2010 estimated that moderate iron deficiency anemia (IDA) affects approximately 610 million people worldwide.[2] Oral iron replacement is the primary treatment strategy for iron deficiency anemia but may be inadequate for some patients due to intolerance, impaired absorption, significant ongoing bleeding, or nonadherence.[3] For these patients, intravenous (IV) iron may be indicated. Compared with oral iron, IV iron can significantly increase levels of hemoglobin, serum ferritin, and transferrin saturation.[4] As of June 2013, there were 5 IV iron products marketed in the United States. While their efficacy is established, the most important safety concern relates to the risk of serious and fatal anaphylaxis,[5-8] which may occur at both first and subsequent exposures.

No sufficiently large randomized trials have been conducted to determine the comparative risk of anaphylaxis for IV iron products. Based on a meta-analysis of published studies of iron dextran, the estimated incidence of anaphylaxis was 0.61%.[9] Although the newer IV iron products are purportedly safer,[10,11] anaphylactic reactions also occur with these products.[8,12] In a randomized, placebo-controlled trial involving more than 2500 patients treated with iron gluconate, the incidence of life-threatening reactions was 0.04%.[9] In another trial of 750 patients treated with ferumoxytol, 1 patient developed anaphylaxis.[13]

To our knowledge, there have been no large population-based observational studies that evaluate the risk of anaphylaxis among different IV iron products. Such a study is important because large head-to-head comparative safety trials to detect rare adverse reactions like anaphylaxis may not be feasible. The purpose of this study was to compare the risk of anaphylaxis among patients receiving different IV iron products in a large, nondialysis, US Medicare patient population.

Methods

Study Population

This study used a retrospective new user cohort design. Patients enrolled in fee-for-service Medicare Part A (hospitalization) and Part B (office-based care) between January 2003 and December 2013 entered the IV iron new user cohort on the date of their first outpatient claim with a Healthcare Common Procedure Coding System (HCPCS) code for an IV iron product (index date). Patients were included in the study if on their index date they were not receiving dialysis, were continuously enrolled in Medicare A and B for the previous 12 months, had no IV iron exposure in the preceding 12 months, and were exposed to only 1 type of IV iron product. Also, patients who had a claim for a blood transfusion on the index date or a diagnosis of anaphylaxis in the 30 days before the index date were excluded. Since ferumoxytol received US Food and Drug Administration (FDA) approval in mid-2009, analyses involving this agent were limited to the period from January 2010 to end of study (December 2013). This study was approved by the Research Involving Human Subjects Committee of the FDA prior to initiation. Patient consent was waived because the study used deidentified health care claims data.

Exposure of Interest

The primary comparison of interest was the use of dextran vs nondextran IV iron products. A secondary analysis compared anaphylaxis risk between iron dextran and 3 approved nondextran products individually (iron gluconate, iron sucrose, and ferumoxytol). Although it was not possible to distinguish between the 2 FDA-approved iron dextrans (high-molecular-weight dextran, low-molecular-weight dextran) based on claims data during most of the study interval because they shared the same HCPCS code, all iron dextran claims were combined into 1 group.

Outcome Definition and Identification

Cases of anaphylaxis were identified using a predefined, validated algorithm, based on *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis/procedure and HCPCS codes for inpatient and outpatient claims, which was developed using the National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria.[14,15] The algorithm had a positive predictive value (PPV) of 63% for anaphylaxis, and 76% for the composite outcome of anaphylaxis or serious *allergic reaction*, the latter of which was defined as an allergic reaction that is highly likely to evolve into anaphylaxis if untreated. False-positive events identified as anaphylaxis by this algorithm in the validation study included mild allergic reactions, isolated hives, rash, and respiratory distress.[14] This algorithm was used to identify anaphylaxis cases when multiple procedure and diagnosis codes were present (eAppendix 1 in the Supplement). Because IV iron-associated anaphylaxis cases reported from clinical trials and spontaneous adverse events indicate that anaphylaxis generally occurs within a few hours of IV iron administration,[8,12] anaphylaxis cases in this study were limited, for the primary analysis, to only those captured on the same date as the IV iron administration, which may plausibly increase the positive predictive value of the algorithm.

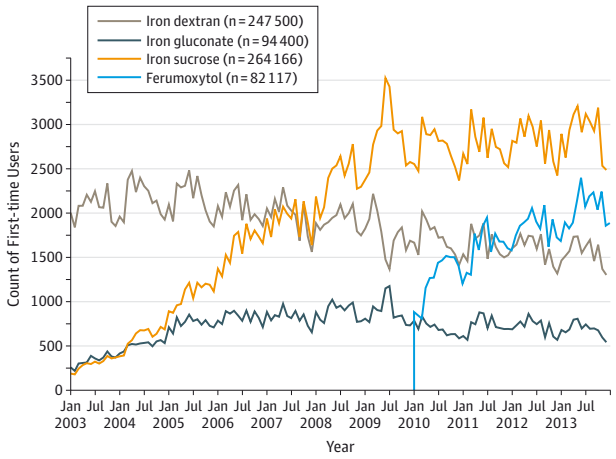
Cohort Follow-up and Censoring

In addition to the analysis of anaphylaxis at the first administration, patients were also followed up to identify the risks of anaphylaxis at subsequent administrations. Follow-up began on index date. Censoring occurred for disenrollment from Medicare Part A or B, switching to another IV iron product, dialysis initiation, occurrence of an anaphylaxis event, death, or end of study (December 31, 2013), whichever occurred first.

Covariates

In addition to age and sex, data on the following potential confounders were collected from Medicare claims during the 12-month period preceding the index date: history of food allergies, history of drug allergy, asthma, chronic obstructive pulmonary disease, coronary heart disease, hypertension, and indications for IV iron use (eAppendixes 2 and 3 in the Supplement). In the sensitivity analysis that included patients with Medicare part D (prescription drug) coverage, concomitant use

Figure 1. Trend of First-Time Use by IV Iron Product



IV indicates intravenous.

of antibiotics, β-blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), and angiotensin-converting enzyme inhibitors was also included.[16,17]

Statistical Analysis

The risk of anaphylaxis and corresponding 95% CIs was calculated for each IV iron product and for the combined nondextran products.[18] Imbalances in baseline characteristics between treatment groups were assessed using standardized mean differences (SMDs). Multivariable logistic regression was used to estimate the risk of anaphylaxis at first administration after adjusting for imbalanced covariates. The Tukey range test was used to adjust for multiple comparisons.[19] The 95% CIs of the adjusted odds ratios (ORs) were estimated based on likelihood ratio tests. The combined nondextran group was used as the reference group when compared with iron dextran. Iron sucrose was used as the reference group for comparisons involving individual IV iron products. Because IV iron products differ by iron dose per administration, the cumulative risk of anaphylaxis was analyzed based on a clinically relevant repletion level of iron (1000 mg) achieved within 12-weeks per recommended dose and schedule. First, the number of exposures necessary to achieve an iron repletion of 1000 mg were obtained by calculating the average number of administrations required for each IV iron product (eTable 1 in the Supplement). Under the assumption that the first administration carried a higher risk of anaphylaxis than subsequent administrations, logistic regression was used to model risk at the first administration. Poisson regression was used to model risk of subsequent administrations. The risk of anaphylaxis with 95% CIs for each treatment regimen was calculated by multiplying the observed number of exposures needed to receive 1000 mg of iron with the risk of anaphylaxis at each administration.

Prespecified sensitivity analyses examined the robustness of the results to variations in the outcome definition, including (1) anaphylaxis cases diagnosed up to 2 days after IV iron administration, (2) anaphylaxis or death occurring on the same day as IV iron administration, (3) cases only meeting anaphylaxis criteria A and B as defined in eAppendix 1 in the Supplement, and (4) restricting the population to patients with Medicare Part D information to account for potential imbalance on relevant concomitant medications. Furthermore, following the approval of ferumoxytol, a generic code J3490 (unclassified drugs) was used temporarily for reimbursement before a specific HCPCS code was assigned. We also conducted sensitivity analysis that removed ferumoxytol users who had a J3490 code during the period of July 2009 through December 2009. $P < .05$ was considered the threshold for statistical significance. All tests were 2-sided. All analyses were performed using SAS version 9.2 (SAS Institute Inc) and R 3.0.2 (R Foundation for Statistical Computing).

Results

There were 247 500 iron dextran and 440 683 nondextran new IV iron users during the study period. New iron dextran use decreased slightly over time, while nondextran use increased, particularly for iron sucrose. Ferumoxytol use began following its 2009 marketing approval (**Figure 1**). At baseline, patients receiving dextran or nondextran IV irons were comparable with age, sex, race, and relevant health conditions except for coronary heart disease and hypertension (**Table 1**). The products differed with respect to the underlying conditions leading to IV iron administration, reflecting differences in FDA-approved indications for use (iron dextran is approved for use in broad iron deficiency anemia indications and nondextran products are approved only for use in patients with chronic kidney disease). Among the individual nondextran products, baseline demographics and anaphylaxis-related characteristics were similar, except for the ferumoxytol cohort, which had the highest proportion of patients with chronic kidney disease (60%) and lowest proportion of patients with gastrointestinal tract and genitourinary tract bleeding (12%) (eTable 2 in the Supplement).

Table 1. Baseline Characteristics for Incident Users Receiving Iron Dextran and Nondextran Intravenous Iron (2003-2013)

	No. (%) of Patients		
	Iron Dextran (n = 247 500)	Nondextran Intravenous Iron (n = 440 683)	Standardized Mean Difference
Baseline Characteristics[a]			
Age, mean (SD), y	73.2 (11.3)	74.0 (11.4)	0.07
Sex			
Men	83 312 (33.7)	167 097 (37.9)	0.09
Women	164 188 (66.3)	273 586 (62.1)	0.09
Race			
White	214 962 (86.9)	374 436 (85.0)	0.05
Black	23 683 (9.6)	48 449 (11.0)	0.05
Asian	1718 (0.7)	4222 (1.0)	0.03
Hispanic	4231 (1.7)	6926 (1.6)	0.01
Other/unknown	2906 (1.2)	6650 (1.5)	0.03
Regions			
Northeast	25 935 (10.5)	86 661 (19.7)	0.26
Midwest	50 782 (20.5)	119 670 (27.2)	0.16
South	135 108 (54.6)	169 783 (38.5)	0.33
West	35 106 (14.2)	63 529 (14.4)	0.01
Other	569 (0.2)	1040 (0.2)	0.00
Indications			
Anemia			
CKD	53 141 (21.5)	233 229 (52.9)	0.69
GI/GU bleeding	53 681 (21.7)	63 956 (14.5)	0.19
Other	140 678 (56.8)	143 498 (32.6)	0.50
Conditions			
Asthma	33 179 (13.4)	60 044 (13.6)	0.01
COPD	72 391 (29.2)	132 620 (30.1)	0.02
Coronary heart disease	101 419 (41.0)	207 127 (47.0)	0.12
Depression	41 481 (16.8)	77 570 (17.6)	0.02
Drug allergy	16 151 (6.5)	33 355 (7.6)	0.04
Food allergy	958 (0.4)	1968 (0.4)	0.01
Hypertension	204 701 (82.7)	394 991 (89.6)	0.20
Beneficiaries With Part D Enrollment[a]			
No. of patients	83 627	211 132	
Concomitant medications			
NSAIDs	5977 (7.1)	10 404 (4.9)	0.09
Antibiotics	1916 (2.3)	5420 (2.6)	0.02
β-Blockers	27 616 (33.0)	86 856 (41.1)	0.17
ACE inhibitors	20 692 (24.7)	52 376 (24.8)	0.00

Abbreviations: ACE, angiotensin-converting enzyme; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GI/GU, gastrointestinal tract and genitourinary tract; NSAIDs, nonsteroidal anti-inflammatory drugs.

[a] Data on concomitant medications were collected for those patients who were enrolled in Medicare Part D (prescription drugs) in 2007-2013.

There were 274 anaphylaxis cases identified at first exposure to an IV iron product. The risk for anaphylaxis was 68 per 100 000 persons (95%CI, 57.8-78.7/ per 100 000) in the iron dextran group compared with 24 per 100 000 persons (95% CI, 20.0-29.5 per 100 000) in the nondextran IV iron group. The OR was 2.6 (95% CI, 2.0-3.3 $P < .001$), after adjustments for age, indication, history of coronary heart disease, and hypertension. Compared with iron sucrose, both iron dextran and iron gluconate were associated with an increased risk of anaphylaxis (OR, 3.6; 95% CI, 2.4-5.4 and OR, 2.0; 95% CI, 1.2-3.5, respectively). Using data from 2010 to 2013, ferumoxytol was also associated with a higher risk of anaphylaxis compared with sucrose (OR, 2.2; 95% CI, 1.1-4.3; **Table 2**). Results of sensitivity analyses were consistent with the main results (eTables 3-6 and eFigures 1-4 in the Supplement). We found less than 1% (548 of 82 117) ferumoxytol users had the generic J3490 code during the June 2009-December 2009 period. Removing these patients had little change to the results (eTable 7 and eFigure 5 in the Supplement).

An additional 170 anaphylaxis events were observed at subsequent IV iron administrations. For all IV iron products, the rate of anaphylaxis was highest at the first administration and decreased thereafter. The decrease was particularly pronounced for iron gluconate and iron sucrose (**Figure 2**). The cumulative risk of anaphylaxis over multiple administrations was highest for iron dextran, followed in decreasing order by

Table 2. Risk of Anaphylaxis at First Administration by Intravenous Iron Products

Intravenous Iron	2003-2013		2003-2013			2010-2013			
	Nondextran	Iron Dextran	Iron Sucrose	Iron Dextran	Iron Gluconate	Iron Sucrose	Ferumoxytol	Iron Dextran	Iron Gluconate
No. of anaphylaxis cases	107	167	45	167	34	21	28	66	16
No. of new users	440 683	247 500	264 166	247 500	94 400	134 836	82 117	77 935	34 029
Rate per 100 000 persons (95% CI)	24.3 (20.0-29.5)	67.5 (57.8-78.7)	17.0 (12.6-23.0)	67.5 (57.8-78.7)	36.0 (25.3-50.9)	15.6 (9.9-24.3)	34.1 (23.1-50.0)	84.7 (66.0-108.4)	47.0 (27.8-78.2)
AOR (95% CI)[a]	1 [Reference]	2.6 (2.0-3.3)	1 [Reference]	3.6 (2.4-5.4)	2.0 (1.2-3.5)	1 [Reference]	2.2 (1.1-4.3)	5.4 (3.0-9.8)	3.0 (1.4-6.5)
P value[b]		<.001		<.001	.005		.02	<.001	.001

Abbreviation: AOR, adjusted odds ratio.

[a] Adjusted for age, indication, coronary heart disease, and hypertension.

[b] *P* value adjusted for multiple comparisons.

ferumoxytol, iron gluconate, and iron sucrose (eFigure 6 in the Supplement). To reach an aggregate iron dose of 1000 mg in the cumulative dose analysis, dextran and ferumoxytol users required 2 administrations on average, whereas sucrose users needed 5 and iron gluconate users needed 7. For cumulative doses of 1000-mg iron administered, as estimated from modeling, iron dextran was also associated with the highest risk of anaphylaxis (82 per 100 000 persons, 95% CI, 70.5- 93.1 per 100 000), whereas iron sucrose was associated with the lowest risk (21 per 100 000 persons, 95% CI, 15.3- 26.4 per 100 000) (**Figure 3**).

The 2 marketed iron dextran products (high-molecular-weight dextran, low-molecular-weight dextran) shared the same HCPCS code during most of the study period. Thus, the individual risk of each iron dextran product could not be fully studied. However, during a brief interval from January 2006 to March 2008, separate HCPCS codes were used for each dextran product. During this period, of 53 914 new iron dextran users, 48 772 (90.5%) received low-molecular-weight dextran and 5142 (9.5%) received high-molecular-weight dextran, suggesting that during the study period, most dextran use in this population was low-molecular weight. Among first administrations of iron dextran during this period, a total of 43 anaphylaxis events were observed, of which 40 (93%) were in those taking low-molecular-weight dextran (eTable 8 in the Supplement).

Discussion

Among more than 680 000 US Medicare nondialysis beneficiaries who initiated IV iron use from 2003 to 2013, iron dextran was associated with increased anaphylaxis risk compared with nondextran formulations at first administration. Among the nondextran products, the risk of anaphylaxis at first administration was higher with both iron gluconate and ferumoxytol than with iron sucrose. Because each IV iron product has a specific recommended dose and schedule of administration, the cumulative risk of anaphylaxis was also calculated based on both the number of administrations and clinically relevant repletion level of iron (1000 mg) achieved within 12 weeks. Both analyses showed iron dextran was associated with the highest cumulative risk of anaphylaxis and iron sucrose with the lowest risk.

All IV iron formulations studied consist of an elemental iron core surrounded by a carbohydrate shell intended to shield the iron core and facilitate iron delivery to the reticuloendothelial system following intravenous administration. The formulations differ from each other in the size of the iron core and the identity and density of the carbohydrate shell.[20] Although iron dextran is asserted to have a greater risk of serious adverse events than the more recently approved nondextran IV iron products, most of the clinical trials that supported the approval of nondextran IV irons used a placebo or oral iron comparator and not iron dextran. Only a few head-to-head trials prospectively compared IV iron formulations, and they were small in sample size, had few or no anaphylaxis events, and were not designed to establish comparative safety.[9,21,22] To our knowledge, the present study represents the largest

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