

Reports to FDA of fatal anaphylaxis associated with intravenous iron products

To the Editor: In the January 2016 issue of AJH, Auerbach and Adamson [1] in their review of the diagnosis and treatment of iron deficiency anemia, state that intravenous (IV) iron is safe to use “in all clinical circumstances including pregnancy.” We note, however, that all IV iron products can cause fatal hypersensitivity reactions including anaphylaxis. During the past five years, the FDA has received 49 reports of death temporally associated with administration of IV iron, 30 of which were adjudicated and determined to be anaphylaxis.

The use of IV iron agents, ferumoxytol, iron dextran, iron gluconate, and iron sucrose, has increased dramatically in the non-dialysis dependent population between 2003 and 2013. The median increase in incident IV iron utilization among Medicare enrolled beneficiaries was 8.1% per year (interquartile range 4.9–15.4%), growing from 32,413 in 2003 to 86,623 in 2013. Figure 1A (Supporting Information) depicts the relative utilization of IV iron by calendar year among patients in the FDA’s Sentinel database, consisting primarily of privately insured patients 20 to 65 years of age; Figure 1B depicts the relative utilization of IV iron by calendar year among patients enrolled in Medicare with supplemental Part D coverage. In both populations, iron dextran utilization decreased in favor of iron sucrose as the predominant IV iron formulation. Ferumoxytol utilization increased starting at market approval in 2009. The increased use of ferumoxytol in the non-dialysis dependent population may have been due in part to the convenience factors of its faster rate of administration (17 seconds at 2009 market approval) and higher amount (510 mg) of iron delivered per dose.

In March 2015, FDA issued a Drug Safety Communication [2] after a search of the FDA Adverse Event Reporting System (FAERS) database identified 79 cases of anaphylactic reactions associated with ferumoxytol administration. Of the 79 cases, 18 were fatal, despite immediate medical intervention and emergency resuscitation attempts. Based on these data, FDA strengthened an existing warning that fatal and serious hypersensitivity reactions can occur, and approved a Boxed Warning, FDA’s strongest type of warning, regarding these serious risks for ferumoxytol. A new Contraindication, against use in patients who have had an allergic reaction to any IV iron product, was also added. The FDA uses contraindications to communicate criteria which identify persons for whom the risk from use clearly outweighs any possible therapeutic benefit. At the same time the ferumoxytol Dosage and Administration section underwent a significant modification with the recommendation to dilute the drug, and administer it over at least 15 minutes, in contrast to the original recommendation to infuse undiluted over 17 seconds.

The FDA has received reports of fatal anaphylaxis reactions with onset of symptoms during or shortly after administration for all of the currently marketed IV iron products. Table I summarizes 30 fatal reports in FAERS from December 2010 through December 2015. Since the Table I data are from spontaneous reports, they must be interpreted cautiously because of potential underreporting, differential product reporting between older versus recently approved IV iron products, and inconsistent quality of information. An additional consideration is that the interpretation of anaphylaxis as a cause of death has inter-observer variability among clinicians, and criteria for adjudicating adverse events of anaphylaxis have changed over time [3]. The reported indication for IV iron use was off-label in 44% of these cases, but it is unknown whether indication for use affects risk for fatal reactions. Death occurred within 24 hr of IV iron exposure in 18 (60%) cases, and within an hour for two cases of ferumoxytol administration, despite interventions in almost all cases. Given the March 2015 labeling recommendation to infuse ferumoxytol over a minimum of 15 minutes, it is noteworthy that 18 of the 19 patients who received IV iron by push administration received ferumoxytol, but also that three deaths associated with ferumoxytol occurred following an infusion of at least 15 minutes. Since deaths occurred after the first, second, and third administrations of IV iron, the risk of fatality may exist at any dose.

A recent retrospective cohort study conducted by FDA researchers using Medicare data [4] suggested the risk of anaphylaxis may differ among IV iron products, and the risk was significantly higher for iron dextran compared to iron sucrose. Published analyses of post-marketing spontaneous reports [5] have also identified potential differential risks among IV iron products, but the limitations of spontaneous reports cited above apply [6]. Hypersensitivity reactions have been reported during clinical trials with IV iron products, but direct comparisons of incidence rates among all currently marketed products are hindered by lack of standardized nomenclature and ascertainment methods for hypersensitivity adverse events. The underlying mechanisms of the anaphylaxis reaction are not understood. The high proportion of reactions with the first IV iron infusion supports a mechanism other than IgE-mediated [7].

We remain concerned about the risk of fatal anaphylaxis with IV iron products, which may differ among products. Although such reactions may be rare, they have the potential to affect the benefit-risk balance of these products, especially when such reactions do not occur with oral iron preparations. In addition to patients with chronic kidney disease, there are disorders with anatomic and functional barriers to oral iron absorption which make oral iron ineffective. In these situations the choice of IV iron is straightforward. The more difficult decisions present when a course of oral iron replacement is started, but a mild to moderate adverse

TABLE I. Selected Demographic and Clinical Characteristics for IV Iron-Treated Patients Who Developed Fatal Anaphylaxis (December 2010–December 2015)

	Patients identified from FDA Adverse Event Reporting System Search (n=30)
Age	
Mean ± Standard deviation	68.7 ± 15.2
Median (Range)	71.5 (20-90)
Gender	
Male/Female	15 (50%)/15 (50%)
Country of origin	
US/non-US	22 (73.3%)/8 (26.7%)
Allergy history	
1 drug	6 (20%)
≥2 drugs	7 (23.3%)
No known drug allergy	9 (30%)
Not reported	8 (26.7%)
Confounding comorbidities^a	
Cardiovascular disease	22 (73.3%)
Renal disease	16 (53.3%)
Pulmonary disease	4 (13.3%)
Convulsions	1 (3.3%)
Not reported	3 (10%)
None	1 (3.3%)
Parenteral iron product	
Ferumoxytol	23 (76.7%)
Ferric carboxymaltose	3 (10%)
Iron gluconate	3 (10%)
Iron sucrose	1 (3.3%)
Iron dextran	0 (0%)
Indication	
Approved use	14 (46.7%)
Unapproved use ^b	11 (36.7%)
Not reported	5 (16.7%)
Dose number	
First dose	9 (30%)
Second dose	9 (30%)
Third dose	3 (10%)
Not reported	9 (30%)
Administration type	
Push (<15 minutes)	19 (63.3%)
Infusion (≥15 minutes)	8 (26.7%)
Not reported	3 (10%)
Symptom onset latency	
During administration	17 (56.7%)
Within 5 minutes of administration	7 (23.3%)
Within 5 to 30 minutes of administration	4 (13.3%)
Within 30 to 60 minutes of administration	1 (3.3%)
After administration (unspecified time to onset)	1 (3.3%)
Death latency	
Less than 24 hr	18 (60%)
<2 hr of starting dose	3/18
<4 hr of starting dose	3/18
Unspecified	12/18
More than 24 hr	10 (33.3%)
Not reported	2 (6.7%)

^a More than one confounding comorbid condition may have been reported per case.

^b Some indications were considered unapproved due to lack of report of qualifying medical history for approved use (e.g., chronic kidney disease).

event (typically gastrointestinal) occurs, which may be an adverse drug reaction. The decision to advocate perseverance with the oral route, or a switch to IV, is done one case at a time. From the safety perspective, the worst justification for choosing IV iron is convenience, although the line between convenience and compliance can be indistinct. All IV iron products carry the warning, “Only administer product when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions.” The

practitioner must ensure, as part of their process for optimizing the benefit risk ratio, that infusing personnel are well educated and practiced in managing these challenging situations.

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Additional Supporting Information may be found in the online version of this article.

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TITLE PAGE

Reply to McCulley et al, Reports to FDA of fatal anaphylaxis associated with intravenous iron products"

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Reply to: Reports to FDA of fatal anaphylaxis associated with intravenous iron products.

We read the correspondence of McCulley et al, with great interest [1]. While we can agree with several of the points made, we take exception to what we consider to be an overestimation of intravenous iron's danger based on inferential evidence, as opposed to prospective studies and high quality meta-analyses. In a recent meta-analysis by Avni et al, [2] comprising 10,391 patients treated with intravenous iron, 4044 oral iron, 1329 no iron and 3335 placebo or no treatment, no safety signal with intravenous iron was reported. Minor infusion reactions were increased with intravenous iron but the adverse event profile was markedly greater with oral iron. The formulations of intravenous iron included in the meta-analysis were iron sucrose, ferric gluconate, low molecular weight iron dextran, ferumoxytol and ferric carboxymaltose. None of the formulations was found to be more or less likely to cause a serious adverse event than any of the others. Consistent with these findings, FDA's own publication [3] concluded that absent head to head studies it is impossible to determine any relative rates of adverse events among available formulations using current reporting mechanisms.

While we appreciate that "49 deaths temporally associated with the administration of intravenous iron were adjudicated and determined to be anaphylaxis," we believe the surrogates for anaphylaxis used in the adjudication preclude credible conclusions as to etiology of the events. One of us (MA) reviewed all of the reports of adverse events with intravenous iron to the Serious Adverse Event Reporting System via Freedom of Information from January 2007 to November 2010. It was impossible to determine which adverse events were associated with which form of iron dextran, whether or not there was premedication or not and, most importantly, whether or not there was intervention for minor infusion reactions with diphenhydramine or vasopressors. These kinds of intervention can convert a minor, self-limited reaction which resolves without treatment into a serious adverse event, and the event will be mistakenly attributed to the intravenous iron. This concern is at least in part supported by the study of Barton et al, [4] which reported that the majority of perceived adverse events with the administration of intravenous iron were due to premedication with diphenhydramine. Nonetheless, as we share the authors' concern about the risk of fatal anaphylaxis, albeit extremely rare, we endorse the use of an algorithm [5] which incorporates our recommendations for the management of minor reactions (Figure 1).

The reports of increased anaphylaxis and death with ferumoxytol are of concern. While we applaud the inclusion of their reference #6 [5] which reports the limitations of spontaneous adverse events reporting, the authors fail to mention the Weber effect which is relevant to the data with ferumoxytol reported in their letter. The reference stated "it was expected that the study findings would show evidence of an initial surge in the use of ferumoxytol, as there tends to be with most newly marketed agents, and that this would be associated with increased adverse event reporting due to the Weber effect." Consistent with this conclusion, the Freedom of Information review revealed 36 serious adverse events reports in the 31 day period from October 10-November 10, 2010. Further supporting these

conclusions, at that time the FDA approval for ferumoxytol allowed a 510 mg bolus to be administered in not less than 17 seconds. We believe this rapid infusion was ill-considered, and the side effect profile as a result of the rapid administration appears to be consistent with elevated levels of labile free iron [7] and not anaphylaxis [8]. One of us (MA) has administered more than 2500 doses of ferumoxytol. The first 90 were administered in 17 seconds. Three episodes of hypotension occurred. There were no deaths or hospitalizations. The remaining doses were administered over 90-180 seconds. No clinically significant adverse events have been observed. Subsequently, FDA's new recommendation to administer ferumoxytol as a 15 minute infusion should mitigate the overwhelming majority of labile free iron reactions.

Consistent with our observations, is an outcomes analysis in hemodialysis centers comparing ferumoxytol to other intravenous formulations comprising 17,958 patients during 6433 person years, which reported no difference in serious adverse events [9], and two prospective, randomized trials comparing ferumoxytol to iron sucrose comprising 767 patients which also reported no difference [10,11].

While it is possible that the "risk of anaphylaxis may differ among intravenous iron products" we strongly disagree that the "risk of anaphylaxis is significantly higher for iron dextran compared to iron sucrose" [12]. All prospective and intra-institutional observational studies published to date show no difference in safety among the available formulations. In the reported analysis only Medicare codes were used. Dialysis patients were excluded, eliminating the lion's share of those who received iron sucrose in the US, as well as the majority of subjects who received low molecular weight iron dextran during the study period. Examples of excluded patients who often receive intravenous iron are those who are pregnant, with heavy uterine bleeding, inflammatory bowel disease and bariatric surgery. However, more importantly, from the authors' own data in their supplemental material on line, a significantly lower death rate was reported with iron dextran compared to the other formulations. Table 1 shows the significantly decreased rate of anaphylaxis on the day of administration. These data are statistically significant ($P=0.04$) and, for all intents and purposes, contradict the conclusion that iron dextrans have higher rates of anaphylaxis than other formulations. Our interpretation is supported by a recent publication from a KDIGO iron management position paper, which reported that, if serious adverse events are not observed after several minutes following parenteral iron administration, such reactions are unlikely to occur [13]. Lastly, as pointed out by the authors, there was an inability to distinguish between high and low molecular weight forms of iron dextran, the former known to be associated with a markedly higher risk of serious adverse events. Fortunately, high molecular weight iron dextran is no longer available.

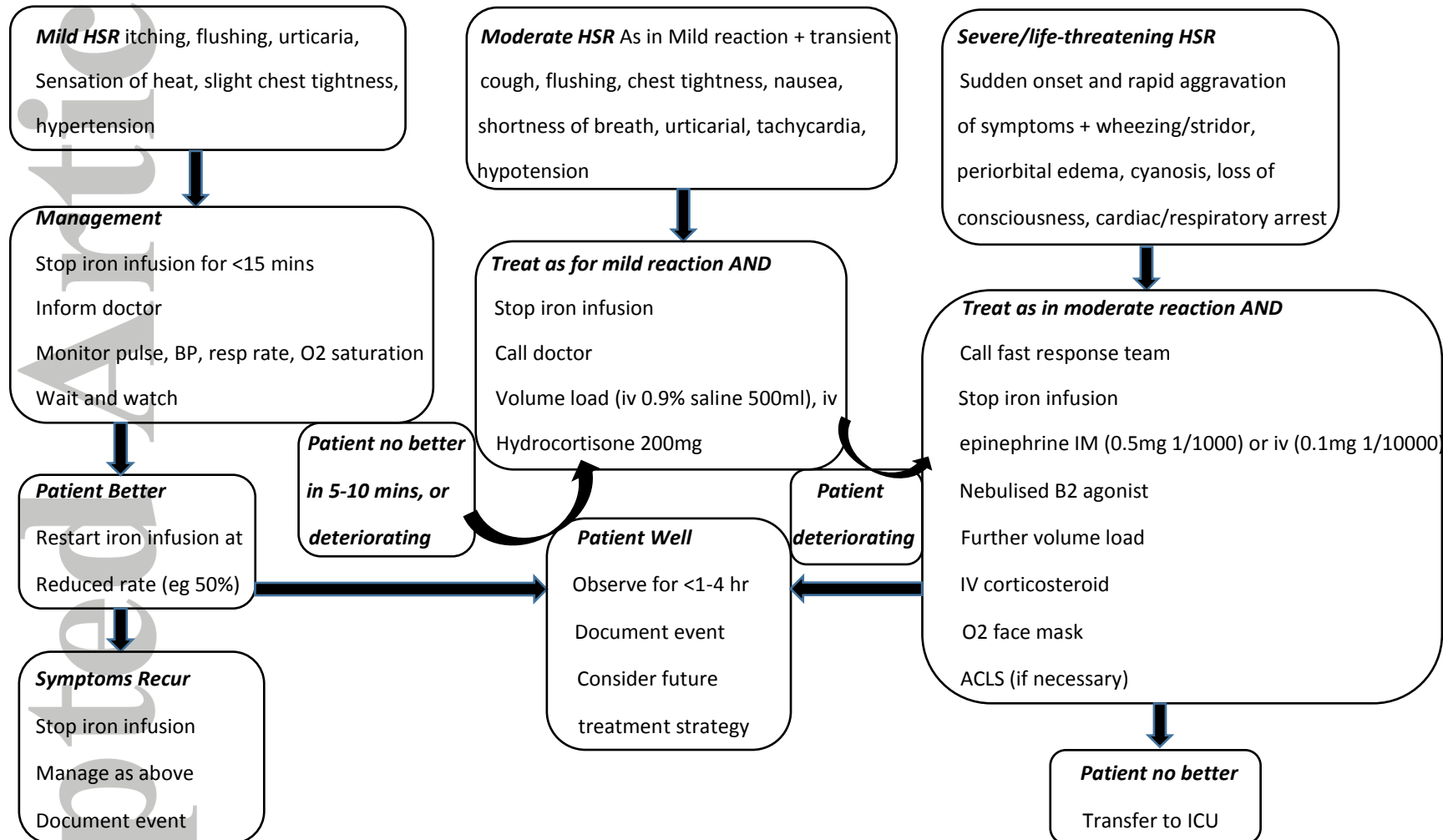
Finally, we agree that convenience is not a justification for choosing intravenous iron over oral iron *in the proper clinical setting*. We agree that for patients with no co-morbidities who tolerate oral iron and are adherent, oral iron may be effective and it is inexpensive and readily available. However published evidence suggests that up to 70% of those for whom oral iron is prescribed will report significant gastrointestinal adverse side effects [14]. For those patients who are intolerant of, or unresponsive to, oral iron, or with medical conditions in which oral iron is ineffective or inappropriate (e.g., heavy uterine bleeding or hereditary hemorrhagic telangiectasia; inflammatory bowel disease, following gastric

bypass procedures [Roux-en-Y or biliopancreatic diversion], then intravenous administration is preferred. Parenteral iron is not just superior in these settings, it is a necessity [15]. Exaggerating the adverse side effects of parenteral iron on the basis of suspect data is not only counterproductive but potentially harmful to patients who otherwise might benefit greatly.

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Treatment of Iron Reactions



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Risk of Fatal Anaphylaxis React on Day of Intravenous Iron Administration

	Non-dextran iron	Iron dextran	Iron sucrose	Iron gluconate	Ferumoxytol
"Anaphylaxis" on day of administration	107	167	45	34	28
Fatality on day of administration	36	10	19	11	6
No. of patients	440 683	247 500	264 166	94 400	82 117
Rate of "anaphylaxis" per 100,000 patients	24.3	67.5	17.0	36.0	34.1
Rate of fatality per 100,000 patients	8.2	4.0	7.2	11.7	7.3

P=0.04 as calculated by Poison-based test. Comparison of fatality rate per 100,000 patients who received iron dextran versus all other products.

Table adapted from Wang C et al, JAMA 2015; 314, 2062-2068