Intravenous Iron Therapy: Re-administration after Prior Adverse Reaction

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Background: Intravenous (IV) iron therapy is performed in community practices and hospitals with modern formulations when oral administration becomes impractical. Effective replacement of iron is important for the treatment of iron deficiency and anemia. Can IV iron be rechallenged in individuals with a history of adverse reactions? This review is to explore the challenge of this, when clinically indicated.

Methods: After performing a literature search, five studies (combined total sample number=1,006) for re-exposure of IV iron to individuals with a history of past reactions were identified, observed, and analyzed. Re-exposure included reactions ranging from mild to moderate and few cases of severe type.

Results: The majority (>80%) of IV iron rechallenges were tolerable, safe, and successful without major serious incidents. There were no reports of major reactions (severe hypersensitivity reactions or anaphylaxis) in these re-exposures.

Conclusion: Re-administration of IV iron therapy in patients with a previous adverse reaction is plausible, with benefit and risk stratification. A rechallenge would depend on the nature and degree of the adverse reaction and use of alternative formulations. Rechallenge to a previous severe hypersensitivity reaction or anaphylaxis with the same product has not been reported in these studies. Evidence on the benefit of premedication use is conflicting and requires further studies.

Keywords: Intravenous Iron; Iron Infusion; Intravenous Iron Reactions; Rechallenge of Intravenous Iron; Re-administration of intravenous iron; Fishbane Reaction

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INTRODUCTION

Iron is an essential micronutrient and an important element for body function. Iron infusion has been performed with modern formulations to treat iron deficiency (ID) and iron deficiency anemia (IDA) when oral iron becomes intolerant, unresponsive, unsuitable, or nonadherence. ID and IDA are ubiquitous in both developed and developing regions, affecting mostly women of reproductive age, young children, the elderly, and individuals with chronic diseases/inflammation. Can iron infusions rechallenge occur safely in an individual with a history of reactions due to intravenous (IV) iron? This review explores the challenges of providing IV iron therapy in the context of past reactions, where clinically indicated.

Iron has various generic formulations, each of which is unique. Its reaction to a specific product may therefore not necessarily imply that the patient will react to another compound. More importantly, the vast majority of IV iron reactions are minor transfusion-related (e.g., fishbane) and non-immunoglobulin E (IgE)-mediated (complement activated-related pseudo-allergy, CARPA). There are several non-dextran IV iron formulations, such as iron sucrose, ferric carboxymaltose, ferric dersiomaltose (also known as iron isomaltoside), and ferumoxyl. Currently, iron polymaltose and low-molecular-weight dextran, although low-cost, are less utilized because of the requirement for test dosing and a longer infusion duration.

Reports of adverse effects (AEs) from IV iron are variable, and depend on the nomenclature used, data source, and study type. Nonetheless, reactions with modern formulations are low, and serious or true anaphylaxis is described as extremely rare. Minor or less severe reactions generally occur at a rate of one in 100 infusions. Severe hypersensitivity reactions (SHR) or anaphylaxis for non-dextran have been suggested to occur in 0.024% (24/100,000) and 0.018% (7.5/40,000) of cases, respectively. Oregon multi-cohort study, based on two documented epinephrine use among 35,737 infusions, yielded 0.005%. A larger study (2005) described true anaphylaxis as occurring in less than 1:200,000 (after exclusion of old dextran-iron). Table 1 summarizes the AEs of IV iron use, simplifying with major (SHR or anaphylaxis), and minor/less severe reactions. The Fishbane reaction resulting from free labile iron nanoparticles is described as the most common type, and is usually transient and resolves spontaneously. The CARPA reaction is hypothesized to occur with rapid exposure to IV iron, which activates the complement system (C3a and C5a) with anaphylatoxin production, leading to a hypersensitivity reaction with variable intensity. It is recognized that the fishbane reaction and other transfusion reactions are often difficult to distinguish clinically from allergic reactions/anaphylaxis (IgE-mediated) and subsequently heighten the anxiety of professionals and patients, leading to extra or unnecessary interventions.

METHODS

The literature search was performed in PubMed, Google Scholar, ResearchGate and ScienceDirect with the search string “intravenous iron reactions” for English articles. Studies without rechallenge, re-exposure, or re-administration with past reactions were excluded. Five studies were identified with a combined total of re-exposure infusion number 1,006. Table 2 lists and analyzes the studies comparing re-exposure to IV iron with past reactions.

RESULTS

The overall results in Table 1 demonstrate a satisfactory sample and outcome, with tolerance, safe, and successful in the majority (>80%) of the rechallenge.

In an Australian study, 69 patients with a history of past reactions

<table>
<thead>
<tr>
<th>Table 1. Adverse effects/reactions of intravenous iron use</th>
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<tbody>
<tr>
<td><strong>I. Major reactions</strong></td>
</tr>
<tr>
<td>Severe hypersensitivity reactions or anaphylaxis: extremely rare but can be life threatening if not managed properly. As per World Allergy Organization, anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. Severe anaphylaxis is characterized by potentially life-threatening compromise in airway, breathing and/or the circulation, and may occur without typical skin features or circulatory shock being present. The typical manifestations include in respiratory (laryngeal oedema/stridor, bronchospasm/wheezes, shortness of breath), and/or circulatory (hypotension/shock/collapse), and/or gastrointestinal (severe crampy abdominal pain, repetitive vomiting), and/or skin/mucosa (angioedema, urticaria). Major reactions imply to Ring &amp; Messmer grade &gt;3.</td>
</tr>
<tr>
<td><strong>II. Minor or less severe reactions/ effects (isolated or combined)</strong></td>
</tr>
<tr>
<td>A. Non-allergic related:</td>
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<tr>
<td>1) Fishbane reaction: flushing/redness of face and neck, and sensation of stiffness or pain in face, chest or back (truncal myalgia) with or without arthralgia</td>
</tr>
<tr>
<td>2) Non-specific symptoms: dizziness, headache, dysesthesia</td>
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<tr>
<td>3) Injection site reactions: pain, discoloration of skin</td>
</tr>
<tr>
<td>4) Delayed symptoms of 1–2 days post-infusion: chills and fever, headache, arthralgia, myalgia, urticaria/rash, angioneurotic oedema</td>
</tr>
<tr>
<td>5) Transient hypophosphatemia may also occur, particularly with ferric carboxymaltose. A few case reports for enduring hypophosphatemia exist, especially in those who require frequent infusion.</td>
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<tr>
<td>B. Allergic related:</td>
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<tr>
<td>6) Mild to moderate allergic reactions (Ring &amp; Messmer grade 1–3): urticaria, angioedema, abdominal pain, vomiting, tachycardia, mild-moderate hypotension, and bronchospasm</td>
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(from mild to moderate and few severe types) were rechallenged with the same (9 [13%]) and alternative iron products (60 [87%]); these rechallenges were found to be largely tolerated, safe, and successful (98%).³⁻¹³ However, no exact data supplied, a relatively satisfactory outcome without major reactions (SHR or anaphylaxis) was reported in a multi-cohort study in Oregon, in which participants were administered the same (majority, 755 [86%]) and alternative preparations (118 [14%]) in 873 cases.²⁻¹³ Interestingly, this study exposed reaction rate elevation 68% (same product use) versus 21% (alternative product use) which was compounded by premedication use as well. The other three studies from Europe (the bottom three of Table 1) with small sampling also reported successful re-exposure in 58%–90% participants with past reactions ranging mild to moderate and few severe types.¹²⁻¹⁵ Lower satisfactory percentage (58%) in the study by Steveling-Klein et al.¹³ was affected by use of same culprit product in majority participants (24/36 [67%]). To note “reactions”, studies number 2 to 5 utilized Ring & Messmer grading scale (grade 1–4), and top number one (Oregon) applied severe adverse events (SAE, defined by the use of epinephrine within 24 hours post-infusion) with the rest as non-SAE; “tolerance, safe and successful” in all these studies seemed to imply no reaction or lesser reaction without major incidents (SHR or anaphylaxis). Those intolerant or unsuccessful cases were reported no reaction or lesser reaction without major incidents (SHR or SAE; “tolerance, safe and successful” in all these studies seemed to imply no reaction or lesser reaction without major incidents (SHR or anaphylaxis). Those intolerant or unsuccessful cases were reported

None of these five studies reported severe hypersensitivity reactions or anaphylaxis. IV, intravenous; LMWD, low molecular weight dextran; ISC, iron sucrose; FCM, ferric carboxymaltose; FOT, ferumoxytol; IPM, iron polymaltose; FDM, ferric dersiolamultose; IIM, iron isomaltoside; NA, not available.

Table 2. Re-exposure of IV iron versus past reaction studies

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Study type</th>
<th>Total no. of IV iron used</th>
<th>Reaction rate</th>
<th>No. of re-exposure</th>
<th>Success/tolerance rate</th>
<th>Formulations used</th>
<th>Patient type &amp; general comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arastu et al.³ (2022) (Oregon/USA)</td>
<td>Retrospective</td>
<td>35,737</td>
<td>3.9% (1,389)</td>
<td>873</td>
<td>No exact data supplied*</td>
<td>LMWD, ISC, FCM, FOT</td>
<td>Adult patients; 755 (86%) with same product and 118 (14%) alternative product</td>
</tr>
<tr>
<td>Stejnovic et al.¹² (2021) (Australia)</td>
<td>Retrospective</td>
<td>13,509</td>
<td>1.4% (195)</td>
<td>69</td>
<td>68 (98%)</td>
<td>IPM, FCM, FCM</td>
<td>Adults; 9 (13%) with same product and 60 (87%) alternative product</td>
</tr>
<tr>
<td>Steveling-Klein et al.¹³ (2021) (Europe)</td>
<td>Prospective</td>
<td>59</td>
<td>NA</td>
<td>36</td>
<td>21 (58%)</td>
<td>ISC, FCM</td>
<td>Adults; in allergy center; 24 (67%) with same product and 12 (33%) alternative product</td>
</tr>
<tr>
<td>Morales Mateluna et al.¹⁶ (2017) (Europe)</td>
<td>Prospective</td>
<td>31</td>
<td>NA</td>
<td>18</td>
<td>15 (83%)</td>
<td>ISC, FCM</td>
<td>Adults; in allergy center; 11 (61%) with same iron product and 7 (39%) alternative product</td>
</tr>
<tr>
<td>Wesström¹⁵ (2020) (Europe)</td>
<td>Retrospective</td>
<td>213</td>
<td>4.7% (10)</td>
<td>10</td>
<td>9 (90%)</td>
<td>IM (=FDM)</td>
<td>Pregnant women; all (100%) with same product IIM</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1,006</td>
<td>82% (without Oregon’s number)</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

None of these five studies reported severe hypersensitivity reactions or anaphylaxis. IV, intravenous; LMWD, low molecular weight dextran; ISC, iron sucrose; FCM, ferric carboxymaltose; FOT, ferumoxytol; IPM, iron polymaltose; FDM, ferric dersiolamultose; IIM, iron isomaltoside; NA, not available.

*No exact data available for successful rate (but concluding safe and useful role without major incidents/reactions), and more reactions if same product and premedication are used.

DISCUSSION

Although rechallenge is generally well-tolerated and safe without serious incidents, re-administration with same product seemed to demonstrate increasing reaction incidents, compared with alternative-product use group, which was evident in the Oregon multi-cohort study¹³ and the study by Steveling-Klein et al.¹³ Furthermore, it is suggested that potential risk factors such as a fast rate of infusion, multiple item/drug allergies, severe atopy/asthma, taking beta blockers or angiotensin converting enzyme inhibitor, mastocytosis, and even the anxiety of professionals be carefully evaluated in every infusion.⁹⁻¹²,¹⁵ An alternative product for history of hypersensitivity reactions,” was brought under question by several later studies, indicating a lack of supportive evidence.¹²⁻¹⁴,¹⁷ Of note, there were a lack of studies on the re-exposure of individuals with prior severe hypersensitivity reactions or anaphylaxis to the same IV iron products; however, the re-exposure of such individuals to alternative preparations was encountered but in small and limited numbers—three cases in Australia (grade 4: two with documented bronchospasm and one with bronchospasm plus multisystem involvement)¹³ and three cases in Switzerland (grade 4: two with angioedema, urticaria, and shock, and one with cardiovascular shock).¹⁴ Encouragingly in the event of simple Fishbane reactions, several studies have consistently reported that resuming the infusion at a slower rate is tolerated and safe even in the same setting, after the infusion has been halted for 10–15 minutes and the symptoms have subsided.⁵⁻⁷,¹³,¹⁵
mild reactive symptoms, especially from North America studies where diphenhydramine is primarily used.3,4,11) The Oregon study highlighted 23-fold rise of associated reactions among cases of premedication in participants in comparison with non-premedicated group (38.6% versus 1.7%).3) In contrast, in an Australian study with premedication (42 [61%]), where promethazine is primarily used, negative side-effects from premedication were not reported.12) Premedication was not employed in three European studies. We were unable to find studies on chlorpheniramine, a commonly used antihistamine in Asia and Europe. Steroid use lacks randomized control data as per Cochrane, but no harmful effects have been reported.20) Theoretically, steroids are known to be useful for immune-related reactions (IgE or complement-mediated).

In conclusion, this study further strengthens the extremely rare occurrence of SHR and anaphylaxis following iron infusion. Rechallenge of IV iron therapy can be considered to have an array of both benefits and risks. Using both the same and different preparations that originally caused a reaction has been found to be tolerated and safe in the case of fishbanes and mild-to-moderate reactions (non-severe hypersensitivity reactions or anaphylaxis). However, rechallenge with alternative compounds appeared to be more favorable. A rechallenge to prior SHR or anaphylaxis with the same product has not been found in this review and is likely to remain unwarranted. Caution is required in patients with a history of severe hypersensitivity reactions or multiple high-risk factors, even when using different products. However, the use of premedication is controversial and requires further investigation.

This review, based on data available to date (October 2022), may be limited by the limited number of rechallenges and a lack of randomized control studies. It may also be marginally constrained by the non-uniform categorization of reactions among institutions/scholars. However, it provides an overall beneficial role for the retrial of iron infusion despite past reactions if indications exist. This study also addresses and counters the long stigma of fear associated with IV iron therapy in the medical community and adds to the growing safety data of modern formulations.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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