Hypersensitivity reactions to iron products: 10-year experience in a Portuguese tertiary Centre

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To the Editor,

Iron products (IP) have been increasingly used in recent years and constitute the first-line treatment for iron deficiency anemia (1). Although hypersensitivity reactions (HSR) to IP are rare and the risk of anaphylaxis with the currently available iron formulations has been shown to be significantly lower compared to iron dextran (2,13–15), there is still a concern regarding the safety of these products, with cases of fatal outcome

reported in the literature (2,3). Here, we evaluate the safety of controlled re-administration of IP in patients with previous hypersensitivity reactions to these drugs.

We performed a retrospective review of patients referred to the Immunoallergology Department in a tertiary hospital for suspected HSR to IP, from 2011 to 2021. The demographic and clinical characterization of a total of 18 patients (mean age 45.6±14.3 years) is summarized in Table I. We observed a higher prevalence of female patients (83%), likely due to the higher frequency of treatment with IP among women (1). Regarding relevant past medical history, six patients (33%) reported previous reaction(s) to non-IP drugs, a similar prevalence found by Steveling-Klein *et al.* in a group of 22 adult patients out of 59 (37%) (4). Three patients were atopic (16%) and two presented with inflammatory diseases (sarcoidosis and inflammatory bowel disease; 11%). Interestingly, only 67% reported previous exposure to IP (Table I).

The IP most frequently involved in hypersensitivity reactions was ferric carboxymaltose (FCM) in 12 patients (63%), followed by oral non-specified iron formulation in four patients (21%) and iron sucrose (IS) in three (16%). One patient presented HSR to both FCM and IS. The severity of reactions was categorized according to the Ring and Messmer Grading Scale for anaphylactic reactions. The majority of the reactions were classified as grade I (n=11, 58%). Grade II occurred in two HSR (11%) and grade III in five (26%), comparable to the distribution reported in the literature (4). One patient (5%) reported an immediate reaction with cyanosis, dyspnea, hypoxemia and circulatory arrest, categorized as grade IV, two minutes after receiving FCM administration. Interestingly, intravenous IP were associated with increased severity of reactions. Drug allergy, atopy, mastocytosis, severe asthma/eczema, severe cardiac or respiratory disease, fast infusion rate, old age and concomitant systemic inflammatory disease have been identified in the literature as risk factors for increased risk and/or severity of IP

hypersensitivity reactions (4,5). In contrast, patients in our population with atopy did not present significantly different severity compared to non-atopic patients, nor did patients with previous hypersensitivity reactions to non-IP drugs (P=0.154 and P=0.086, respectively; Mann-Whitney Test, Graph-Pad Prism v5.01). Age was also not correlated to severity (r=-0.19, P=0.44; Spearman Correlation).

During diagnostic work-up, skin prick and intradermal tests with the suspected and/or alternative IP were performed on 12 patients, with FCM (Ferinject®, 50mg/mL; n=10), and/or IS (Venofer®, 20mg/mL; n=11). We found a positive result only in one patient (ID test with IS, 100-fold dilution), in agreement with results from other studies on HSR to IP. These results are in line with the most likely putative mechanism of HSR to non-dextran-derived IP: complement activation-related pseudo-allergy (2,4,6,7). In contrast to the rare IgE-mediated HSR, self-limited transitory flushing and truncal myalgias, denominated as *Fishbane* reactions, are common and often misdiagnosed as hypersensitivity reactions (2). Importantly, in both IgE and non-IgE HSR mechanisms, desensitization has been reported to be effective, although time-consuming (8–12).

In clinical practice we may consider three alternative strategies in the management of patients with HSR to IP: graded re-administration, desensitization, and use of premedication prior to IP.

In our study, the outcomes of these strategies were registered (Table II). Patients to whom iron was re-administered gave oral and written informed consent.

IP re-administration was successfully conducted in 15 patients (ten IS and five FCM; using premedication, antihistamines ± corticosteroids, in ten patients), in two of them with the culprit IP. IP desensitizations were conducted according to Mariana Castells' 12-step protocol (12) and performed in three patients, (seven IS and two CMF), all with

the culprit agent. Desensitization was tolerated by two patients (one IS and one CMF), one of them being the patient with a positive IDT test to IS. The third patient, with a history of severe iron deficiency anemia secondary to inflammatory bowel disease, failed to complete all seven desensitization protocols (six IS and one CMF). She experienced grade III HSR during the tolerance inducing protocols, which prevented her from achieving the total required therapeutic dose.

The scarcity of cases of hypersensitivity reactions to IP, documented during a 10-year activity in an Allergy Clinic from a tertiary hospital, is in agreement with the rare prevalence of these reactions reported in the literature (3). Detailed clinical history and implementation of risk minimization measures, particularly slow infusion rates (iron sucrose 200mg/3h and ferric carboxymaltose 500mg/3h), are decisive for the management of hypersensitivity reactions and are mostly sufficient to minimize the occurrence of mild and *Fishbane* reactions, these latter frequently misdiagnosed as allergic reactions (13).

Our results stand out against the position of the European Medicines Agency, stating that intravenous iron products are contraindicated in patients with known serious hypersensitivity to any parenteral iron product (19). In fact, our study supports recent observations regarding the safety of re-challenge with an alternative IP, and even with the culprit formulation, which are generally well tolerated in mild and moderate reactions (4,6,20). Additionally, the absence of HSR upon re-administration of an alternative IP, regardless of the use of premedication (eight with premedication; five without premedication), underlines the difficulty in determining the benefit of premedication. Re-administration of the culprit IP was performed, and tolerated, in two patients, with premedication. Notably, the evidence supporting premedication with antihistamines is uncertain, as their vasoactive effects can rather be misinterpreted as

anaphylaxis symptoms, however, this is still recommended as a strategy to minimize the risk of reaction to IP (3,13,16–18).

The authors highlight that the implementation of a low-reactogenic administration protocol in clinical practice, consisting of a slow infusion rate, corresponding to an infusion rate three and six times slower than the recommended for ferric carboxymaltose and iron sucrose, respectively, should be encouraged. Recommendations regarding premedication should be addressed in further studies. Patient management should be individually decided according to the severity of the HSR, however, the authors herein report that the majority of patients tolerated the re-administration of an alternative or even the same IP, emphasizing the safety of this approach.

Bibliography

1. Nathell L, Gohlke A, Wohlfeil S. Reported Severe Hypersensitivity Reactions after Intravenous Iron Administration in the European Economic Area (EEA) Before and After Implementation of Risk Minimization Measures. Drug Saf. 2020;43(1):35–43. doi:10.1007/s40264-019-00868-5

2. McCulley L, Gelperin K, Bird S, Harris S, Wang C, Waldron P. Reports to FDA of fatal anaphylaxis associated with intravenous iron products. Am J Hematol. 2016;91(12):E496–7.

3. Tomer A, Amir B, Alon G, Hefziba G, Leonard L, Anat GG. The safety of intravenous iron preparations: Systematic review and meta-analysis. Mayo Clin Proc. 2015;90(1):12–23. doi:10.1016/j.mayocp.2014.10.007

4. Steveling-Klein EH, Mateluna CM, Meienberg A, Hartmann K, Bircher A, Scherer Hofmeier K. Management of Hypersensitivity Reactions to Nondextran Iron Products: New Insights Into Predisposing Risk Factors. J Allergy Clin Immunol Pract. 2021;9(6):2406-2414.e2. doi:10.1016/j.jaip.2021.01.009

5. Rampton D, Folkersen J, Fishbane S, Hedenus M, Howaldt S, Locatelli F, et al. Hypersensitivity reactions to intravenous iron: Guidance for risk minimization and management. Haematologica. 2014;99(11):1671–6.

6. Morales Mateluna C, Scherer Hofmeier K, Bircher A. Approach to hypersensitivity reactions from intravenous iron preparations. Allergy. 2017;72(5):827–30.

7. Szebeni J, Fishbane S, Hedenus M, Howaldt S, Locatelli F, Patni S, et al. Hypersensitivity to intravenous iron: Classification, terminology, mechanisms and management. Br J Pharmacol. 2015;172(21):5025–36.

8. Di Girolamo A, Albanesi M, Loconte F, Di Bona D, Caiaffa MF, Macchia L. Desensitization in Iron Product Allergy. Acta Haematol. 2020;143(5):496–9.

9. Chapman E, Leal D, Alvarez L, Duarte M, García E. Two case reports of desensitization in patients with hypersensitivity to iron. World Allergy Organ J. 2017;10(1):1–4.

10. Demir S, Olgac M, Unal D, Gelincik A, Colakoglu B, Buyukozturk S. A practical

and successful desensitization protocol for immediate hypersensitivity reactions to iron salts. Int Arch Allergy Immunol. 2014;165(2):100–3.

11. De Barrio Fernández M, Fuentes V, Tornero P, Sánchez I, Zubeldia J, Herrero T. Anaphylaxis to oral iron salts. Desensitization protocol for tolerance induction. J Investig Allergol Clin Immunol. 2008;18(4):305–8.

12. Castells M. Rapid Desensitization for Hypersensitivity Reactions to Medications. Immunol Allergy Clin North Am. 2009;29(3):585–606.

13. Achebe M, DeLoughery TG. Clinical data for intravenous iron – debunking the hype around hypersensitivity. Transfusion. 2020;60(6):1154–9.

14. Trumbo H, Kaluza K, Numan S, Goodnough LT. Frequency and Associated Costs of Anaphylaxis- and Hypersensitivity-Related Adverse Events for Intravenous Iron Products in the USA: An Analysis Using the US Food and Drug Administration Adverse Event Reporting System. Drug Saf. 2021;44(1):107–19. doi:10.1007/s40264-020-01022-2

15. Wang C, Graham DJ, Kane RC, Xie D, Wernecke M, Levenson M, et al. Comparative risk of anaphylactic reactions associated with intravenous iron products. JAMA - J Am Med Assoc. 2015;314(19):2062–8.

16. Wang C, Wong S, Graham DJ. Risk of Anaphylaxis With Intravenous Iron Products: In reply. JAMA - J Am Med Assoc. 2016;315(20):2232–3.

17. Lim W, Afif W, Knowles S, Lim G, Lin Y, Mothersill C, et al. Canadian expert consensus: management of hypersensitivity reactions to intravenous iron in adults. Vox Sang. 2019;114(4):363–73.

18. Bircher AJ, Auerbach M. Hypersensitivity from intravenous iron products. Immunol Allergy Clin North Am. 2014;34(3):707–23.

19. EMA-CHMP. New recommendations to manage risk of allergic reactions with intravenous iron-containing medicines. Eur Med Agency. 2013;(EMA/579491/2013):2–3.

20. Stojanovic S, Graudins L V., Aung AK, Grannell L, Hew M, Zubrinich C. Safety of Intravenous Iron Following Infusion Reactions. J Allergy Clin Immunol Pract. 2021;9(4):1660–6. doi:10.1016/j.jaip.2020.11.028

Table I. Clinical characterization of patients with hypersensitivity reactions to iron products.

Characteristics	Total (N = 18)
Gender, n (%)	
Female	15 (83.3)
Age, years	
Mean ± SD (minimum - maximum)	45.6 ± 14.3 (15.0-72.0)
Relevant medical history, n (%)	
Non-IP drug allergy	6 (33.3)
Atopy	3 (16.7)
Rhinitis	3 (16.7)
Asthma	1 (5.6)
Sarcoidosis	1 (5.6)
Inflammatory bowel disease	1 (5.6)
Previous exposure to IPs, n (%)	
Exposure without reaction	12 (66.7)
No exposure	6 (33.3)

IP, Iron products; N, total number of patients; SD, standard deviation.

Table II. Detailed characterization of hypersensitivity reactions to iron products.

Characteristics	Total (N = 18)
Culprit IP, n (%)[†]	19 (100)
Ferric carboxymaltose	12 (63.2)
Oral IP preparation	4 (21.1)
Iron Sucrose	3 (15.8)
Grade of reaction, n (%)*,[†]	
I	11 (57.9)
Oral IP preparation	4
Ferric carboxymaltose	7
II	2 (10.5)
Iron Sucrose	2
III	5 (26.3)
Ferric carboxymaltose	4
Iron Sucrose	1
IV	1 (5.3)
Ferric carboxymaltose	1
Positive IP skin tests / Total, n[†]	
Ferric carboxymaltose	0/10
Iron Sucrose	1/11
IP re-administration, n	**15**
Ferric carboxymaltose	5
Premedication	4
Alternative IP / Culprit IP	3/2
Tolerated	5
Iron Sucrose	10
Premedication	6
Alternative IP / Culprit IP	10/0
Tolerated	10
IP desensitization, n[†]	**9**
Patient 1	**1**
Ferric carboxymaltose	1
Premedication	1
Alternative IP / Culprit IP	0/1
Tolerated	1
Patient 2	**1**
Iron Sucrose	1
Premedication	1
Alternative IP / Culprit IP	0/1
Tolerated	1
Patient 3	**7**
Ferric carboxymaltose / Iron Sucrose	1/6
Premedication	7
Alternative IP / Culprit IP	0/7
Tolerated	0

N, total number of patients; *According to Ring and Messmer Grading Scale; [†] More than 1 procedure per patient.