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

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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

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.

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 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®, 50 mg/mL; n = 10), and/or IS (Venofer®, 20 mg/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

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.

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 200 mg/3h and ferric carboxymaltose 500 mg/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 anaphy-

laxis 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.

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None.

Contributions

CV, JC: conceptualization, formal analysis, writing - original draft. CV, JC, JV, CJC, MP, ASS, AL, SLS, EP: data curation, writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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