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CHARACTERISTICS OF ADVERSE DRUG REACTIONS ASSOCIATED WITH IRON DRUGS AND RESULTS OF DRUG PROVOCATION TESTS: A SINGLE-CENTER EXPERIENCE IN TERTIARY CARE

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Abstract

Objectives: Iron drugs are frequently prescribed in primary care for the treatment of iron deficiency anemia, while parenteral drugs are used in patients with malabsorption or intolerance to oral drugs. Gastrointestinal side effects are common after oral iron, whereas hypersensitivity reactions (HSRs) may occur less frequently but with both oral and parenteral drugs.

Materials and Methods: We retrospectively evaluated 39 adult patients (2021–2024) referred to the Immunology and Allergic Diseases Clinic with suspected iron drug allergy. Clinical features, reaction severity, and results of alternative or diagnostic drug provocation tests (DPTs) were analyzed.

Results: The study included 36 females and 3 males, with a median age of 40 years (range 20–77). Initial reactions were IgE-mediated HSRs in 82% and non-allergic side effects in 18%. Most IgE-mediated HSRs (79%) were mild (Grade 1), with 12% classified as severe (Grade 3). The most frequently suspected drug was iron carboxymaltose (43.6%). DPTs were performed with alternative iron drugs in 82% and for diagnostic purposes in 18% of cases. Negative results were obtained in 87% of DPTs, while 13% were positive; all positive reactions were mild (Grade 1) and most commonly associated with iron carboxymaltose. Desensitization with iron carboxymaltose was successfully performed in three patients without alternative treatment options.

Conclusion: Although non-allergic side effects are more common, IgE-mediated HSRs to iron drugs remain a clinically significant concern due to their potential severity, including rare anaphylaxis. Cutaneous symptoms were the most frequent presentation. Any skin manifestations during iron therapy should prompt discontinuation of the drug and referral to an allergy specialist for further evaluation.

Keywords: Anemia, adverse drug reactions, hypersensitivity reactions, non-allergic side effects.

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Introduction

Iron deficiency anemia (IDA) is the most common type of anemia, resulting from decreased hemoglobin (Hb) production due to insufficient iron in the body. The most common causes are inadequate iron intake, increased need (e.g., during pregnancy or growth), chronic blood loss (especially from the digestive system or menstrual bleeding), and absorption disorders.[1,2] As well as symptoms such as fatigue, pallor, dizziness, and shortness of breath, other signs may include brittle nails, hair loss, and pica. A diagnosis can be made through tests such as a complete blood count, serum iron, ferritin, and total iron-binding capacity. Treatment traditionally involves taking oral iron supplements. Nevertheless, parenteral iron drugs may be preferred in cases of intolerance, absorption disorders, or severe deficiency.[3-6] Given that IDA is one of the most frequent conditions encountered in primary care, family physicians are often the first to prescribe iron drugs and to monitor treatment.

Iron drugs are generally classified into two forms based on the oxidation state of the iron they contain: +2 (Fe^{2+}, ferrous) and +3 (Fe^{3+}, ferric). The drugs in the Fe^{2+} (ferrous) form — like ferrous sulfate, ferrous gluconate, and ferrous fumarate — are better absorbed in the small intestine and are consequently the first choice in IDA. In contrast, ferric forms— such as iron polymaltose complex and ferric hydroxide–sucrose complexes — are more stable and cause fewer gastrointestinal side effects, but their absorption is generally lower. Ferric forms may be preferred, especially in patients with gastrointestinal intolerance. For proper absorption, the ferric form must be reduced to the ferrous form in the body; therefore, the presence of gastric acid is important for this conversion.[6-10]

Adverse drug reactions (ADRs) are undesirable and detrimental effects that occur with normal doses of medicines. These reactions fall into two main categories: type A and type B. Type A reactions constitute the vast majority of cases and can affect anyone who takes the drug. They are predictable and dose-dependent. These reactions are triggered by toxic, adverse, and indirect effects of drugs as well as drug interactions. The most common type A reactions of oral iron drugs include nausea, abdominal pain, constipation, diarrhea, indigestion, and dark stool color.[11,12] Type B reactions are also known as drug hypersensitivity reactions (HSRs). Type B reactions, which account for approximately 15-20% of ADRs, are both unexpected and dose-independent. Immune-mediated HSRs are divided into two subgroups: immunoglobulin E (IgE)-mediated and T-cell-mediated. IgE-mediated (immediate-type) type iron drug HSRs occur within the initial 1–6 hours and typically present as urticaria and/or angioedema (AE). Iron drug-induced anaphylaxis is also considered part of this category.[12-15] T-cell-mediated immune HSRs associated with iron drugs are uncommon. These HSRs typically happen hours to days after the administration of the drug.[16]

This study aimed to evaluate the demographic characteristics, types, and severity of ADRs and the results of diagnostic and alternative drug provocation tests (DPTs) in patients presenting to our clinic with ADRs to iron drugs.

Materials and Methods

Study design

In our study, we retrospectively evaluated the characteristics of reactions and developing symptoms experienced by 39 adult patients (between 2021 and 2024) referred to the Immunology and Allergic Diseases Clinic with ADRs related to iron drugs, as well as the results of alternative or diagnostic DPTs. Data for the study were obtained from the hospital information management system in accordance with the principles of the Declaration of Helsinki, following approval from the local ethics committee. This study was approved by Ankara Bilkent City Hospital Ethics Committee (approval number: TABED 2-25-1151). The review and approval process was conducted blindly to ensure impartiality.

The following information was obtained from patient medical records: age, sex, reaction, and time of symptom onset, method of administration of the iron drug, atopy history, other allergies and diseases, and treatments received. Patients under 18 years of age and patients with an ADR to a drug other than iron were excluded from the study. Patients with T-cell-mediated immune HSRs delayed were not included in the study.

Evaluation of adverse drug reactions to iron drugs

When patients referred from other clinics to the Immunology and Allergic Diseases Clinic with suspicion of HSR due to iron drugs were evaluated, the reactions of patients presenting with only gastrointestinal symptoms were classified as type A (non-allergic). Reactions that occurred within 1–6 hours after drug intake and were characterized by clinical features such as urticaria, pruritus, angioedema, shortness of breath, wheezing, hypotension, or anaphylaxis, and/or a positive drug test result, were classified as type B (immediate-type HSRs).[11]

Severity of immediate-type hypersensitivity reactions to iron drugs

The signs and symptoms of HSRs were categorised as follows: Cutaneous: flushing, pruritus, urticaria and angioedema, cardiovascular: chest pain, tachycardia, presyncope, syncope and hypotension, respiratory: nasal-ocular symptoms, dyspnoea, wheezing and oxygen desaturation; throat tightness; gastrointestinal symptoms such as nausea, vomiting, diarrhoea and abdominal pain; and atypical manifestations such as fever/chills, back and neck pain and numbness/weakness.[17]

The severity of immediate-type HSRs to iron drugs was evaluated according to Brown's grading system, which classifies reactions into three grades based on clinical features. Grade 1 (mild) includes cutaneous manifestations such as urticaria and/or angioedema; Grade 2 (moderate) involves additional mild respiratory, cardiovascular, or gastrointestinal symptoms; and Grade 3 (severe) represents life-threatening respiratory and/or cardiovascular symptoms.[17]

Diagnostic drug testing protocols with iron drugs

Patients with no contraindications to DPTs were given detailed information about the test, after which consent was obtained from each patient. The DPTs were performed only in a clinical setting equipped for emergency interventions and by experienced physicians. Antihistamines were discontinued five days before DPTs, and steroids were discontinued approximately two weeks before, depending on the dose and strength of the drugs.

Skin tests were performed according to the ENDA/EAACI protocol.[18] Skin prick test (SPT) with the iron drug was a diagnostic procedure used to evaluate IgE-mediated immediate-type HSR. During the SPT, a non-irritant concentration of the parenteral iron solution, as previously determined, was applied to the forearm or back. Then, a small puncture was made in the skin using a sterile lancet. Approximately 15–20 minutes later, the resulting swelling and redness were evaluated to determine the test result. These were then compared with positive and negative controls (histamine and physiological serum, respectively). The intradermal testing (IDT) was performed, starting with lower concentrations and increasing cautiously up to the non-irritant concentration of parenteral iron solution.

The DPT was the gold-standard diagnostic method used to confirm or rule out a suspected HSR to an iron drug. The diagnostic DPT was primarily used when the skin test was negative, but the patient's medical history indicated continued suspicion of an allergy to the iron drug. If the relationship between the HSR and the iron drug was very strong and the baseline HSR was severe, a test was performed using an alternative iron drug. The DPT was conducted using incremental doses of the suspected drug, starting from 1/100 of the therapeutic dose, followed by stepwise increases to 1/10, 1/2, and the full dose at 30–60 minute intervals. Patients were closely monitored after each dose, and the test was immediately discontinued if any HSR occurred. After reaching the total cumulative dose, patients were observed for at least two hours. For oral iron drugs, dose escalation was performed orally, whereas for intravenous drugs, infusion rates were gradually increased. In patients with a history of severe anaphylaxis, direct provocation testing was avoided, and alternative approaches or desensitization protocols were applied. Desensitization was used to manage HSRs to the iron drugs, particularly if there were no alternative treatments available or cross-reactions developed with similar drugs. Due to the risk of systemic HSRs, all tests were conducted under the supervision of an allergist.[12,16,18]

Statistical Analysis

Data analysis was performed using the SPSS 11.5 for Windows software package (SPSS Inc., Chicago, IL, USA). Descriptive statistics for nominal data are presented as counts and percentages, and quantitative data are presented either as mean ± standard deviations or medians and minimum-maximum depending on assumptions of normality based on visual (histograms and probability graphs) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). All p-values below 0.05 were considered significant.

Results

General specialties of the study population

In our study, which included 36 female and 3 male patients, the median age [(minimum (min.)-maximum (max.)] (years) was 40 (20-77). A majority of the patients (n=35, 80%) had never smoked, and more than half (n=20, 51.3%) had a university education. No additional comorbidity was found in 64.1% (n=25) of patients, and no additional allergic disease was found in 76.9% (n=30) of patients. The most common comorbid disease in patients (n=5, 12.8 %) was hypertension. The most common accompanying allergic diseases were allergic rhinitis and urticaria, both of which occurred in three patients (7.7%). The demographic characteristics of the patients are shown in Table 1.

Table 1. Demographic characteristics of patients

Parameters	Results
Age (years) [median (min.-max.)]	40 (20-77)
Gender (n, %)	
Female	36 (88)
Male	3 (12)
Smoking history (n, %)	
Yes	4 (10)
No	35 (80)
Educational Status (n, %)	
Primary school	3 (7.7)
Secondary school	3 (7.7)
High school	13 (33.3)
University	20 (51.3)
Occupation (n, %)	
Housewife	16 (41)
Civil servant	12 (30.8)
Retired	6 (15.4)
Student	5 (12.8)
Comorbidity (n, %)	
None	25 (64.1)
Cardiac-hypertension	5 (12.8)
Endocrine	4 (10.3)
Malignancy	3 (7.7)
Gastroesophageal reflüx	1 (2.6)
Rheumatological	1 (2.6)
Additional allergic disease (n, %)	
None	30 (76.9)
Urticaria	3 (7.7)
Allergic rhinitis	3 (7.7)
Beta-lactam allergy	2 (5.1)
Isolated pruritus	1 (2.6)

Evaluation of characteristics during initial adverse drug reactions to iron drugs

Following an evaluation conducted at our clinic, it was determined that 82% (n = 32) of initial ADRs that occurred after the use of the iron drug were determined to be IgE-mediated immediate-type HSRs (type B reactions), while the remaining 18% (n = 7) were identified as non-allergic drug side effects (type A reactions) (Figure 1). The commonest non-allergic side effects (type A reactions) of the iron drugs were heartburn and constipation.

The severity of IgE-mediated immediate-type HSRs (type B reactions) according to Brown's grading system was Grade 1 in 79% (n=26) of patients and Grade 3 in 12% (n=5) (Figure 2). The majority of patients had mild allergic symptoms.

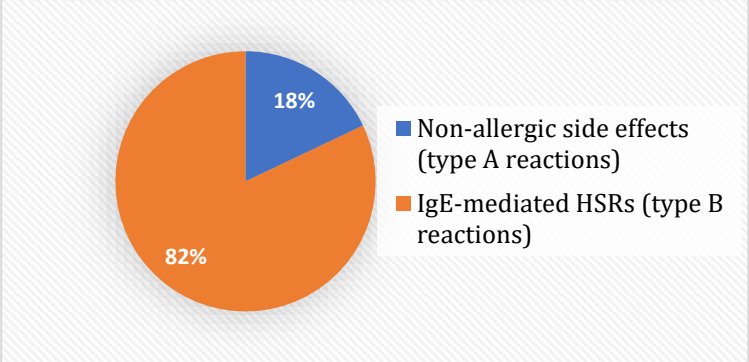

Figure 1. Classification of initial adverse drug reactions to iron drugs

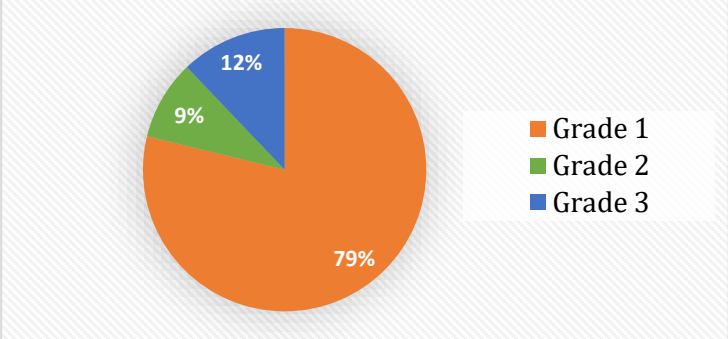

Figure 2. Severity of IgE-mediated hypersensitivity reactions according to Brown's grading system

The median duration of time for initial reactions to occur after drug intake was 60 minutes (min:2–max:1.200). Among the iron drugs referred from other clinics due to suspicion of drug allergy, the most common ones were the ferric (Fe^{3+}) iron forms (n=26, 67%). The most commonly referred iron drug to our clinic due to suspected ADRs was iron carboxymaltose (n=17, 43.6%). The second most common was ferrous (Fe^{2+}) sulphate (n=8, 20.5%). The least common drug is ferric hydroxide sucrose (n=1, 2.5%). The most common system involvement in the initial reaction was only skin (n=28, 71.8%). Erythema and flushing were the most widespread symptoms experienced by the patients. Anaphylaxis was observed in five patients. Although syncope (n = 2, 5.1%) and desaturation (n = 3, 7.7%) were rare symptoms among our patients, HSRs to iron drugs were found to be potentially life-threatening. Adrenaline was administered to 5 patients with anaphylaxis. Patients with grade 1 and 2 HSRs were initially treated with antihistamines only (n = 11, 28.2%) or antihistamines and steroids (n = 18, 46.2%). The characteristics of initial ADRs that developed in patients with suspected iron drug allergy are shown in Table 2.

Table 2. Characteristics of initial adverse drug reactions that developed in patients with suspected iron drug allergy

Parameters	Results
Time to onset of the initial reaction (minutes) [median (min.-max.)]	60 (2-1200)
Form of suspected iron drug (n, %)	
Ferrous (+2)	13 (33)
Ferric (+3)	26 (67)
Number of reactions to the suspected iron drug [median (min.-max.)]	1 (1-3)
Suspected iron drugs (n, %)	
Ferrous sulfate	8 (20.5)
Ferric hydroxide polymaltose	7 (17.9)
Iron carboxymaltose	17 (43.6)
Ferric hydroxide sucrose	1 (2.5)
Ferro fumarate	4 (10.3)
Ferrous glycine sulfate	2 (5.2)
System involvement in the initial reactions (n, %)	
Skin	28 (71.8)
Respiratory	4 (10.3)
Anaphylaxis	5 (12.8)
Gastrointestinal	2 (5.2)
Symptoms in the initial reactions (n, %)	
Flushing	20 (51.3)
Erythema	25 (64.1)
Urticaria	18 (46.2)
Angioedema	14 (35.9)
Dyspnea	9 (23.1)
Desaturation	3 (7.7)
Syncope	2 (5.1)
Tachycardia	6 (15.4)
Hypotension	5 (12.8)
Diarrhea and vomiting	9 (23.1)
Treatments given in the initial reactions (n, %)	
Antihistamine	11 (28.2)
Antihistamine and steroid	18 (46.2)
Adrenaline	5 (12.8)
No treatment	5 (12.8)

Results of diagnostic and alternative drug provocation testing

In our study, the majority of DPTs (n=32, 82%) were performed with alternative iron drugs, while 18% (n=7) were performed for diagnostic purposes. The most commonly used drug in DPTs was ferrous sulfate (n=16, 41%), followed by ferric hydroxide polymaltose (n=8, 20.5%), iron carboxymaltose (n=7, 17.9%), ferric hydroxide sucrose (n=7, 17.9%), and ferrous fumarate (n=1, 2.6%). Negative results were found in 87% (n=34) of the DPTs, and positive reactions were detected in 13% (n=5). All positive reactions were mild (Grade 1),

most frequently associated with iron carboxymaltose (n=4, 80%) and less frequently with ferric hydroxide sucrose (n=1, 20%). Successful desensitization with iron carboxymaltose was performed in 3 patients who had positive test results and required iron therapy and had no alternative treatment options. The results of diagnostic and alternative DPTs are presented in Table 3.

Table 3. Provocation test results with iron drugs

Parameters	Results
Provocation test (n, %)	
Alternative	32 (82)
Diagnostic	7 (18)
Provocation test drugs (n, %)	
Ferrous sulfate	16 (41)
Ferric hydroxide polymaltose	8 (20.5)
Iron carboxymaltose	7 (17.9)
Ferric hydroxide sucrose	7 (17.9)
Ferro fumarate	1 (2.6)
Provocation test result (n, %)	
Positive	5 (13)
Negative	34 (87)
Severity of reaction (n, %)	
Grade 1	5 (100)
Positive test result (n, %)	
Iron carboxymaltose	4 (80)
Ferric hydroxide sucrose	1 (20)
Desensitizing drug (n, %)	
Iron carboxymaltose	3 (100)

Discussion

This study evaluated the demographic characteristics, reaction types, severity, and DPT outcomes in patients with suspected ADRs to iron drugs. Our findings demonstrated that the majority (82%) of ADRs were IgE-mediated immediate-type HSRs (type B reactions), while non-allergic type A reactions accounted for 18% of cases. This distribution highlights that, although gastrointestinal adverse effects are the most frequently reported with oral iron drugs, IgE-mediated immediate-type HSRs are not uncommon and require careful evaluation.[11,13,19,20] Since our study included patients who were referred to the Immunology and Allergic Diseases Clinic and had a high suspicion of drug allergy, we believe that type B reactions were detected more frequently. Many iron drug non-allergic side effects (type A reactions), especially gastrointestinal ones, are well known by physicians and are managed correctly. However, managing IgE-mediated HSRs (type B reactions) remains challenging for many physicians. They often need to consult an allergist to make an accurate diagnosis and develop an appropriate management plan. Therefore, in our study, the rate of IgE-mediated immediate-type HSRs was higher than other non-allergic side effects (type A reactions).

Previous studies have shown that intravenous iron drugs, particularly ferric carboxymaltose and iron sucrose, can trigger immediate mild to severe IgE-mediated immediate-type HSRs. In our study, ferric (Fe^{3+}) forms were implicated more frequently (67%), with ferric carboxymaltose being the most commonly suspected drug (43.6%). This predominance may be linked to its widespread clinical use, parenteral administration route, and potential for rapid systemic exposure, all of which have been reported to increase the risk of hypersensitivity [15,21-24]

Another important result of our study is that the majority of initial reactions (71.8%) involved cutaneous symptoms alone, most commonly erythema and flushing. This supports previous reports that skin-limited presentations are the most common manifestation of IgE-mediated HSRs to iron drugs. Nevertheless, we observed five cases of anaphylaxis, accounting for 12.8% of ADRs. Although rare, severe systemic reactions to iron drugs have been documented in previous studies, highlighting the importance of carrying out intravenous administrations in environments with emergency intervention capabilities.[16,23-25]

The DPTs are the gold standard for confirming or excluding drug hypersensitivity when drug skin tests are negative or inconclusive. In our study, the DPTs were performed with alternative iron drugs in 82% of patients and diagnostic drug challenges in 18% of patients. The overall positivity rate was 13%, with all positive results graded as mild (Grade 1) during the DPTs. This is consistent with the safety profile of well-monitored DPTs reported in previous studies. The high proportion of negative results (87%) further emphasises the importance of objective testing to avoid unnecessary drug avoidance, which can restrict treatment options.[18,22,25,26]

Interestingly, 80% of positive DPT results were observed with ferric carboxymaltose and 20% with ferric hydroxide sucrose. While this may suggest a higher allergenic potential for certain drugs, caution is warranted due to the small sample size and the potential for confounding factors arising from drug usage frequency. Desensitization protocols were successfully implemented in patients requiring continued ferric carboxymaltose therapy, which is similar to the previous reports of the safety of desensitization for intravenous iron drugs.[22-24]

This study has several strengths. Firstly, conducting the study at a tertiary allergy and clinical immunology centre ensures that the obtained data reflect real-life conditions and can be applied directly to daily clinical practice. Second, all cases were meticulously examined, with a detailed clinical history taken and symptoms and reaction severity assessed according to the Brown classification.[17] The safe application of desensitization in cases where there are no alternative treatment options also enhances the clinical value of the study.

The limitations of our study include its retrospective design, single-centre setting, and small sample size, all of which may restrict the generalisability of the results. This study was conducted in a tertiary allergy–immunology center, which may have introduced a referral bias toward more complex or severe cases.

Therefore, the relatively high rate of type B reactions observed in our cohort may not accurately represent the distribution of ADRs in the general population. Furthermore, delayed-type T-cell-mediated reactions were excluded from the analysis, meaning that the findings primarily reflect immediate-type HSR patterns. Future multicentre prospective studies with standardised testing protocols are needed to improve our understanding of the epidemiology, risk factors, and optimal management strategies for both immediate and delayed HSRs to iron drugs.

In conclusion, while non-allergic ADRs (type A reactions) are more common, IgE-mediated immediate-type HSRs to iron drugs are a clinically relevant concern due to their potential severity, including rare cases of anaphylaxis. In our study, ferric carboxymaltose was the drug most frequently implicated, with cutaneous symptoms being the predominant presentation. Therefore, any skin symptoms that develop in a patient taking iron medication should not be ignored. The medication should be stopped immediately. Family physicians and other physicians should be aware of the clinical spectrum of immediate-type HSRs, document any adverse events carefully, and refer suspected cases to an allergy specialist for confirmation and management.

The diagnostic DPTs have proven to be a safe and indispensable diagnostic tool, allowing the confirmation or exclusion of a suspected allergy in appropriate patients and preventing unnecessary medication use. In patients for whom diagnostic DPTs are not available, the DPTs with alternative iron drugs are crucial for maintaining patient continuity of treatment. When alternative treatments are unavailable, desensitization with the iron drug (especially ferric carboxymaltose) can be successfully performed. All physicians should be aware of the possibility of IgE-mediated immediate-type HSRs to iron drugs, especially parenteral drugs, and ensure that administration occurs in settings equipped to promptly recognize and manage severe reactions. We believe this article is a guide for family physicians to refer patients who use iron drugs due to iron deficiency anemia and experience allergic reactions to allergists for management. Further prospective, multicenter studies are needed to elucidate the underlying mechanisms, identify risk factors, and optimize management strategies for iron drug hypersensitivity.

Ethical Considerations: This study was reviewed and approved by the Ethics Committee of Ankara Bilkent City Hospital (approval number: TABED 2-25-1151). The ethics review process was conducted in a blinded manner to ensure objectivity, and conflict of interest declarations were also independently reviewed by the committee.

Conflict of Interest: The authors declare that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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