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Research Article

Treatment protocol with alternative iron drugs in patients with an allergic reaction during iron replacement therapy

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Abstract

In our study, we aimed to show that alternative iron salts containing different additives are safe to use in patients who have type 1 hypersensitivity reactions to iron drugs and need iron replacement therapy.

Materials and methods: Between January 2022 and June 2022, patients who had previously developed type 1 hypersensitivity reactions with iron preparations and needed iron replacement were included in the study. The study was designed retrospectively. Skin tests were first performed on patients to demonstrate a type 1 hypersensitivity reaction. If skin tests were negative and there was no history of life-threatening anaphylaxis, oral provocation tests were continued. If the absence of variability in symptoms and perimeter values, the drug allergy test was considered negative.

Results: Twenty-two patients were included in the study. Twenty-one of the patients were female and one was male. Iron deficiency anemia was found in nine patients, and low iron stores in thirteen patients without anemia were found. Type 1 hypersensitivity reaction developed with Iron 3 Carboxymaltose in 7 patients, Iron 2 Sulfate in 5 patients, Iron 2 Glycine in 4 patients, Iron 3 Hydroxy Polymaltose in 4 patients, Iron 2 Fumarate in 1 patient and Iron 3 Hydroxide Sucrose in 1 patient. Allergy tests with all alternative iron drugs containing additional additives were negative.

Conclusion: If patients with allergic reactions cannot be referred to allergy clinics, we think that oral iron salts with different additives can be used after the first dose is given in the hospital under general anaphylaxis precautions. We show that oral iron salts containing different additives can be safely used.

More Information

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Introduction

Iron deficiency affects a large part of the world's population, especially women of childbearing age, children, and individuals living in low- and middle-income countries. In the meta-analysis, it was stated that the prevalence of iron deficiency anemia in women was 20%. In 2020, low ferritin (< 30 ng/mL) was detected in 389 (8.7%) of 4451 people over 50 years of age in the UK without anemia. The prevalence of non-anemic iron deficiency was higher in women than in men (10.9% *vs.* 6.3%) [1].

The choice between oral and intravenous (IV) iron therapy depends on a number of factors, including the severity of anemia, the cost of different iron replacement products and the patient's ability to tolerate oral iron preparations. Oral iron is generally effective, inexpensive, and safe. Therefore, oral iron is preferred more often. However, up to 70% of patients using oral iron (especially iron 2 sulfates) report gastrointestinal side effects [2].

IV iron therapy has the potential to cause allergic reactions, including life-threatening anaphylaxis. Different from IV iron preparations, allergic reactions to oral iron preparations are rarely reported [3]. Few cases with isolated ferrous (iron 2) or isolated ferric (iron 3) hypersensitivity have been reported in the literature. However, allergies to additional (sweetener and adjuvant) additives are observed more frequently [4].

Additives may cause cross-reactivity among themselves. Cross-reactivity may be observed between iron 2 sulfate, iron 2 ascorbates, and iron 2 lactate [5].

Due to the risk of hypersensitivity, we performed skin prick tests (SPT) and intradermal tests (IDT) with iron preparations, before oral provocation tests with iron drugs containing different additives. For SPT, we used the drugs that are commercially available in the form of syrup with iron (II) glycine sulfate, iron (II) fumarate and iron (III) poly maltose, undiluted. For the IDT dose, we used iron (II) glycine sulfate, iron (II) fumarate and iron (III) poly maltose complex at dilutions of 1:1000, 1:100, and 1:10 [6].

In our study, we performed oral provocation tests (OPT) after skin tests with alternative iron salts containing different additives to patients who experienced type 1 hypersensitivity reactions with iron drugs and needed iron replacement therapy. We aimed to show that alternative iron salts containing different additives are safe to use in patients who have type 1 hypersensitivity reactions to iron drugs and need iron replacement therapy.

Materials and methods

Between January 2022 and June 2022, patients who had previously developed type 1 hypersensitivity reactions with iron preparations and needed iron replacement were included in the study. All patients were over the age of 18 and iron replacement therapy was approved by the internal medicine or hematology clinic. The study was designed retrospectively. The patients' hemoglobin (HB) value was measured as g/L, hematocrit (HCT) value as %, mean corpuscular volume (MCV) value as fL, red cell distribution width (RDW) value as %, ferritin value as ng/ml. Informed consent was obtained from all patients before skin tests and OPT. In skin tests, histamine (10 mg/mL) was used as a positive control and sterile 0.09% saline was used as a negative control. The test was considered positive if the induration diameter was ≥ 3 mm more than the negative control in skin tests. All OPT was performed in hospital conditions and after emergency response facilities were provided. If skin tests were negative and there was no history of life-threatening anaphylaxis, OPT was continued. Vital signs and perimeter values of the patient were recorded before OPT. Vascular access was established in patients with a previous history of anaphylaxis. In the absence of variability in symptoms and perimeter values, the drug allergy test was considered negative and it was confirmed that the patient could safely take the drug.

This study was approved by the institutional review board, College of Medicine Research Center, Erzurum Training and Research Hospital (reference number 2022/15-151). All patient data were confidential and used for research purposes only, and all the patients were coded with a serial number without mentioning their names, and informed consent was obtained from the patients. This study was conducted in accordance with the Declaration of Helsinki.

There are no relevant financial or non-financial competing interests to report.

Export IBM SPSS Statistics for data analysis. 23.0 (IBM Co., Armonk, NY, USA), was used.

Results

Twenty-two patients were included in the study. Twenty-one of the patients were female and one patient was male. The median age of the patients was 36,4 ± 8,36 years, and the patients were between 18 and 45 years old. Iron deficiency anemia was found in nine patients, and low iron stores without anemia were found in thirteen patients. The mean hemoglobin (HB) value of the patients was 11.9 g/L, and the hemoglobin value of the patients ranged between 9.1 g/L and 14.5 g/L. The mean hematocrit (HCT) value of the patients was 36.2% and the hematocrit value of the patients was between 12.9% and 44.7%. The mean mean corpuscular volume (MCV) value of the patients was 77.2 fL, and the MCV value of the patients ranged from 64.3 fL to 87.9 fL. The mean red cell distribution width (RDW) value of the patients was 19.6%, and the RDW value of the patients was between 13.5% and 43.6%. The mean ferritin value of the patients was 4.6 ng/ml, and the ferritin value of the patients ranged between 1.1 ng/ml and 9.5 ng/ml. 4 patients had a history of allergy to other drugs besides iron allergy. Of these patients, 2 had quinolone allergy, 1 patient had a contrast material allergy, and 1 patient had a cephalosporin allergy. Demographic and laboratory characteristics of the patients are indicated in Table 1. Tryptase value was studied with the preliminary diagnosis of systemic mastocytosis in patients with multiple drug allergies. Blood tryptase values ranged from 4.6 µg/L to 6.9 µg/L. After treatment with iron salts, 21 patients had a history of urticaria/angioedema and 1 patient had a history of anaphylactic shock. Type 1 hypersensitivity reaction developed with Iron 3 Carboxymaltose in 7 patients, Iron 2 Sulfate in 5 patients, Iron 2 Glycine in 4 patients, Iron 3 Hydroxy Polymaltose in 4 patients, Iron 2 Fumarate in 1 patient, and Iron 3 Hydroxide Sucrose in 1 patient. SPT and IDT performed with alternative iron drugs were negative in 21 patients. Skin test could not be performed in 1 patient due to dermographism. An oral provocation test (OPT) with alternative iron salts was performed on all patients. OPT was administered in 3 periods equivalent to 5 mg, 20 mg and 50 mg elemental iron at 30-minute intervals. After the last dose of OPT, patients were observed for at least 2 hours. All OPTs were negative. The patients completed their treatment with alternative iron drugs without any problems.

Discussion

According to the definition of the World Health Organization, anemia is defined as hemoglobin (Hb) less than 13 g/dl in men over the age of 15, less than 12 g/dl in women over the age of 15 and who are not pregnant, and less than 11 g/dl in pregnant women. There are two steps in iron deficiency. The first step is defined as the reduction of

Table 1: Patient's demographic and laboratory characteristics.

Patient no	Age	Gander	Allergic iron drug	Reaction	Alternative iron drug	Additional drug allergy	HB (g/L)	HCT (%)	MCV (fL)	RDW-CV (%)	FERRITIN (ng/ml)
1	22	Female	Iron 3 carboxymaltose	Urticaria	Iron 2 Fumarate		10,8	35,1	74,8	18,6	2,1
2	40	Female	Iron 2 Sulfate	Urticaria	Iron 2 Glycine	Quinolone	14,3	44,7	87,5	42,2	9,5
3	19	Female	Iron 2 Fumarate	Urticaria	Iron 2 Sulfate		14,5	43,6	87,9	29,2	9
4	38	Female	Iron 2 Sulfate	Urticaria	Iron 2 Fumarate		12,4	38,1	79,4	13,6	3,9
5	33	Female	Iron 2 Glycine	Urticaria	Iron 3 Hydroxy Polymaltose		12,8	39,1	87,7	43,6	7,8
6	39	Male	Iron 2 Glycine	Urticaria	Iron 3 Hydroxy Polymaltose	Cephalosporin	13,3	43,5	66	17,2	3,7
7	37	Female	Iron 2 Sulfate	Urticaria	Iron 2 Glycine		11,8	39,3	75	14,7	1,8
8	44	Female	Iron 3 carboxymaltose	Urticaria	Iron 3 Hydroxy Polymaltose		10,2	32,2	73,6	18,6	2,6
9	45	Female	Iron 2 Glycine	Urticaria	Iron 2 Sulfate		11,4	37,7	74,2	14,9	4,4
10	26	Female	Iron 3 Hydroxy Polymaltose	Urticaria	Iron 2 Glycine		12,9	39,3	75,7	17,5	4,6
11	37	Female	Iron 2 Sulfate	Urticaria	Iron 2 Glycine		12,3	39.1	80,1	22,9	7
12	38	Female	Iron 3 Hydroxy Polymaltose	Urticaria	Iron 2 Sulfate		11,5	37,3	79,5	13,6	6
13	37	Female	Iron 2 Sulfate	Urticaria	Iron 3 Hydroxy Polymaltose	Quinolone	12	38	83	13,8	5,7
14	41	Female	Iron 3 carboxymaltose	Urticaria	Iron 2 Sulfate		12,5	39,7	79,7	16,4	4,9
15	18	Female	Iron 3 Hydroxy Polymaltose	Urticaria	Iron 2 Sulfate		14,3	42,2	84,6	13,5	6,2
16	34	Female	Iron 3 carboxymaltose	Urticaria	Iron 3 Hydroxide Sucrose		9,1	32,6	64,3	17,5	1,1
17	42	Female	Iron 3 carboxymaltose	Urticaria	Iron 2 Sulfate		9,8	32,5	70	16,9	1,7
18	28	Female	Iron 3 carboxymaltose	Urticaria	Iron 3 Hydroxy Polymaltose		12,2	40,9	71,1	21	4,3
19	36	Female	Iron 2 Glycine	Urticaria	Iron 2 Fumarate		9,8	30,7	70,9	16	1,3
20	18	Female	Iron 3 Hydroxy Polymaltose	Urticaria	Iron 2 Fumarate		12,9	38,5	82,8	14,1	8,1
21	28	Female	Iron 3 carboxymaltose	Anaphylaxis	Iron 2 Sulfate		9,7	32,9	73,4	18,8	3,6
22	35	Female	Iron 3 Hydroxide Sucrose	Urticaria	Iron 2 Sulfate	Contrast Materials	11,6	23,6	78,7	16,3	2,2

the body's total iron. Anemia is not yet present. In the second step, erythropoiesis due to iron deficiency decreases, and iron deficiency anemia (IDA) occurs as a result. Iron salts have low molecular weight and activate the immune system by binding to high molecular weight molecules. Ferric iron salts have a more stable form and are less bound to macromolecules. Therefore, it is less allergenic. However, ferric iron salts are less absorbed from the gut than ferro-iron salts [6]. In our study, 9 patients had an allergic reaction to ferric-iron salts and thirteen patients had an allergic reaction to ferrous-iron salts. While gastrointestinal side effects (nausea, epigastric pain, constipation, etc.) are more common with oral iron preparations, the frequency of allergic reactions is rare with oral iron preparations [7]. Cross-reactions may occur with iron preparations such as ferrous sulfate, ferrous ascorbate, ferrous lactate, and ferrous fumarate [6]. In our study, 1 patient with iron 2 sulfate allergy was given iron 2 fumarates, 1 patient with iron 2 fumarate allergy was given iron 2 sulfates, and no cross-reactions were observed between these molecules.

Different doses are indicated in the literature for skin prick testing with iron preparations. In some studies, the skin prick test was performed with syrup without dilution, while in some studies the skin prick test was performed with a dose of 10 mg/ml [6-8]. In our study, we performed skin prick tests with syrup without dilution. Except for the patient with dermographism, all patients had negative SPTs. It showed that skin prick testing with undiluted iron syrups is not an irritant dose. We performed IDT at 1:1000, 1:100, and 1:10 dilutions of Iron (II) glycine sulfate, iron (II) fumarate, and iron (III) poly maltose complex [6-8]. Except for the patient with dermographism, all IDTs were negative. OPT was performed on all patients because skin tests were negative. OPT was completed in 3 steps at 30-minute intervals. After the test, all patients were kept under observation for at least 2 hours. Patients who did not have an allergic reaction during OPT received treatment for a period of time deemed appropriate by the internal medicine or hematology clinic.

Mastocytosis is a clonal disease characterized by the proliferation and accumulation of mast cells (MC) in different tissues, preferentially skin and bone marrow. Mastocytosis in adults is associated with a history of anaphylaxis in 22% - 49%. Fatal anaphylaxis has been described particularly following Hymenoptera stings, but also occasionally after the intake of drugs such as nonsteroidal anti-inflammatory drugs, antibiotics, opioids, and drugs in the perioperative setting. Nevertheless, mast cell disorders might be ruled out in cases of severe systemic reactions. Careful examination of the skin should accompany the measurement of basal serum tryptase levels. Mastocytosis patients typically have baseline serum

tryptase levels over 20 ng/mL. In our study, the measured serum tryptase levels of all patients who participated and had a history of anaphylaxis were below 11.4 ng/mL [9,10].

Conclusion

Due to the high prevalence of iron deficiency, iron salts are frequently prescribed by doctors. Although gastrointestinal side effects are common, especially in oral iron treatment, allergic reactions can be seen rarely. If patients with allergic reactions cannot be referred to allergy clinics, we think that oral iron salts with different additives can be used after the first dose is given in the hospital under general anaphylaxis precautions. More extensive studies are needed on this subject.

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