CASE REPORTS

Anaphylaxis to Oral Iron Salts. Desensitization Protocol for Tolerance Induction

M de Barrio, V Fuentes, P Tornero, I Sánchez, J Zubeldia, T Herrero

Allergy Department, Hospital General Universitario "Gregorio Marañón", Madrid, Spain

Abstract

Allergies to iron salts are seldom reported. We studied a patient with iron-deficiency anemia who had suffered anaphylactic reactions caused by oral iron salts. An allergy study was performed using single-blind, placebo-controlled oral challenge and skin tests with various iron salts as well as excipients in commercial formulations.
Oral challenges were positive for 2 of the commercial formulations of iron salts. Intradermal tests with ferrous sulphate and ferrous lactate also showed positive results. All of the cutaneous tests using the excipients were negative. A desensitization protocol was designed which enabled us to readminister ferrous sulphate, although antihistamines were necessary to guarantee good tolerance to iron salts.
We report a patient with allergy to iron salts, positive skin tests, and positive controlled challenge. We highlight the desensitization protocol designed to complete the therapeutic management of the anemia.

Key words: Oral iron salts. Anaphylaxis. Desensitization.

Resumen

Las sales de hierro pueden causar infrecuentemente reacciones alérgicas. Estudiamos una paciente diagnosticada de anemia ferropénica con reacciones anafilácticas por sales ferrosas administradas por vía oral. Realizamos estudio alergológico mediante provocación oral simple ciego controlada con placebo y pruebas cutáneas con distintas sales de hierro, así como con los componentes del excipiente de las distintas formulaciones comerciales.
La provocación oral fue positiva con dos preparados comerciales diferentes de hierro. Las pruebas intradérmicas con sulfato y lactato ferroso también fueron positivas. Las pruebas cutáneas con los componentes de los excipientes resultaron negativas.
Elaboramos un protocolo de desensibilización que permitió readministrar a la paciente sulfato ferroso para tratamiento de la anemia, aunque se precisó tratamiento antihistamínico para inducir su tolerancia.
Presentamos una paciente con alergia a sales de hierro, con pruebas cutáneas y provocación oral positivas. Destacamos el protocolo de desensibilización realizado para completar el manejo terapéutico de la anemia.

Palabras clave: Sales de hierro oral. Anafilaxia. Desensibilización.

Introduction

Oral administration of iron salts for iron deficiency treatment is usually well tolerated. Adverse gastrointestinal side effects are the most common. Exanthematous eruptions or anaphylactic reactions following a parenteral iron dextran injection are very uncommon [1].

We report a case of recurrent anaphylactic reaction caused by oral administration of iron salts. We also present the results of the allergy study and a protocol developed for desensitization to ferrous sulphate.

Case Description

A 68-year-old woman with a personal history of hypercholesterolemia, diverticulosis, hiatal hernia, and iron deficiency anemia was referred to our department to be tested for a possible allergic reaction to iron salts. The patient reported that several years previously she had presented with pruriginous papules on her head and trunk 3 days after starting treatment for iron deficiency with an unidentified iron salt. This skin reaction occurred 2 hours after taking the drug, although the symptoms disappeared when antihistamine treatment was initiated and

the drug was stopped. Two years later, papules reappeared at the same site accompanied by hypotension 10 days after she started to take Cromatonbic ferro (ferrous lactate) (Menarini SA, Barcelona, Spain). This reaction occurred 2 hours after the drug had been administered. One year later, she presented with sole itch, urticaria on the trunk, shortness of breath, and dizziness 2 hours after receiving the fourth vial of Cromatonbic ferro. The patient had also been treated with omeprazole and simvastatin and continued to take these drugs with no adverse reactions. No other drugs, suspicious food, physical factors, or insect bites were associated with these reactions. The patient presented persistent signs and symptoms of iron deficiency anemia, with skin and mucosal discoloration, a functional systolic heart murmur, and worsening laboratory values: hemoglobin 8.6 g/dL (12-15.5 g/dL), hematocrit 27.6% (37-47%), mean corpuscular volume (MCV) 55.3 fL (88-99 fL), iron 9 µg/dL (37-145 µg/dL), ferritin 3.4 µg/L (12-200 µg/L), and transferrin 340 µg/dL (200-360 µg/dL).

In a clinical setting requiring drug therapy and in which the drug itself is an unlikely cause of allergic reactions, test dosing or graded challenge is commonly used to determine whether it may be administered safely [2]. Therefore, we obtained the patient's written informed consent, which enabled us to proceed with a single-blind, placebo-controlled oral challenge (SBPCOC). Ferrous sulphate (Ferogradumet) (Abbot Científica SA, Madrid, Spain) was administered initially at 65 mg and increased to 525 mg. Two hours after the administration of this last dose, the patient presented papules on her wrist and back. Placebo challenge was negative. Due to the unusual clinical diagnosis, and with the purpose of checking tolerance to a different ferrous salt, another SBPCOC was performed with ferrous ascorbate (Ferro-Semar) (Semar SA, Barcelona, Spain). Urticaria reappeared when a 275-mg dose of this last drug was reached.

Skin tests were performed with ferrous sulphate and ferrous lactate (Table 1), and with excipients of the commercial formulations. All the products were prepared in our laboratory with the raw materials kindly provided by their manufacturers. Prick tests were negative for both iron salts and excipients. Positive responses were obtained in intradermal tests with ferrous lactate (0.1 mg/mL and 1 mg/mL) and ferrous sulphate (0.01 mg/mL and 0.1 mg/mL) (Figure). The excipients tested proved negative. Intradermal tests performed with ferrous sulphate and ferrous lactate in 15 healthy controls were also negative. There was no evidence of the existence of specific immunoglobulin (Ig) E to ferrous sulphate using the enzyme-linked immunosorbent assay.

Based on the procedures mentioned above, the patient was diagnosed with anaphylaxis due to immediate hypersensitivity to iron salts.

As this patient required treatment with iron salts, she was hospitalized and a protocol for desensitization to ferrous sulphate was designed (Table 2). We started with the highest dose tolerated during the SBPCOC (262.5 mg). Administration on the first day was problem-free and the dose was increased to 393.75 mg on the second day, with the appearance of hives 3 hours later. This same dose was tolerated from the third to the fifth day. On the sixth day, urticaria reappeared and was treated. On the seventh and eighth days, the same dose was administered with no problems. After increasing the dose to 525 mg, on several occasions and on consecutive days, the patient presented scattered papules. On day 13, mild urticaria was accompanied by dizziness, although hypotension was not confirmed. On the following days, we decided to treat the patient with ebastine (10 mg) in the morning and dexchlorpheniramine (6 mg) in the evening prior to administering the ferrous sulphate (525 mg). The patient tolerated this dose and was discharged. Antihistamines were

Table 1. Concentrations of Iron Salts Used in Skin Test

	Ferrous Sulphate	Ferrous Lactate
Prick test	10 mg/mL	10 mg/mL
Intradermal test	0.01-0.1 mg/mL	0.01-0.1- - 1 mg/mL

Table 2. Protocol for Desensitization to Ferrous Sulphate

Day	Dose (mg)	Pretreatment With Antihistamines	Symptoms
1	262.50	No	No
2	393.75	No	Urticaria
3-5	393.75	No	No
6	393.75	No	Urticaria
7-8	393.75	No	No
9-12	525.00	No	Urticaria
13	525.00	No	Urticaria/ dizziness
14	525.00	Yes	No
15-17	525.00	Yes	No
18 and successive[a]	525.00	YES	No

[a] Patient was discharged on the 18th day.

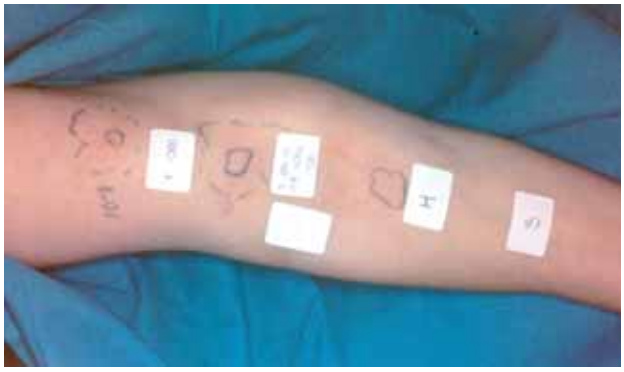

Figure. Intradermal Tests With Ferrous Sulphate

progressively reduced and ebastine (10 mg) was administered on alternate days. During the following weeks of continuous therapy with iron, the patient did not present urticaria at any time. The hemoglobin, hematocrit, MCV, iron level, and ferritin values gradually returned to normal after 10 weeks of treatment. Red cell alterations (anisocytosis, microcytosis, hypochromia, and poikilocytosis) persisted for some time, although the anemia eventually remitted and treatment with iron and ebastine was stopped.

Discussion

Iron salts are seldom responsible for allergic reactions. A few cases of eruptive dermatosis, such as generalized micropapular [3] or pustular exanthema [4], photodermatitis [5], and lymphocytic perivasculitis [6] have been reported. Nevertheless, iron dextran can induce serum sickness-like reactions [7] and delayed hypersensitivity reactions, which manifest as lymphadenopathy, myalgia, arthralgia, fever, and headache [8]. However, very few studies examine mild anaphylactic reactions (pruritus, urticaria, angioedema) or severe anaphylactic reactions (with associated hypotension, cardiovascular shock, bronchospasm, or respiratory failure) after intravenous administration [8,9].

We report an anaphylactic reaction caused by oral iron salts. Positive skin tests and SBPCOC confirmed the diagnosis. To the best of our knowledge, this has not been previously reported in the medical literature. Our patient had several adverse reactions after taking commercial iron salts that had been formulated using different additives and preservatives. This would seem to indicate that iron, rather than any pharmacological excipient, had been the cause of the anaphylactic reactions. This hypothesis was subsequently confirmed by the results obtained from skin tests. Moreover, the results of the study also demonstrated cross-reactivity between different iron salts, in accordance with previous findings [3].

The pathogenesis of anaphylactic reactions to iron dextran has not yet been elucidated. In most reports, these episodes occur after the first contact with the drug. This should support an anaphylactoid origin rather than a truly anaphylactic reaction [9-11]. Novey et al reported a positive basophil histamine release test with iron dextran, but with no other evidence that could support an IgE-mediated hypersensitivity mechanism [10]. In our case, both the positive skin tests with ferrous sulphate and the negative results in the control subjects tested corroborate the specificity of the response and demonstrate the existence of an immediate, possibly IgE-mediated hypersensitivity mechanism. Nevertheless, no IgE could be demonstrated by in vitro techniques. Like most drugs, iron salts are low molecular weight compounds and must be bound to a macromolecular carrier to become immunogenic. Furthermore, in vitro detection of drug-specific IgE antibodies is usually less sensitive than skin testing with the suspected agent.

As in other allergic reactions where the drug is essential for the control of the disease, a desensitization protocol with ferrous sulphate was performed and the therapeutic dose of 525 mg (equivalent to 106 mg of elemental iron) was reached. Although this dose triggered various slight anaphylactic symptoms, it was administered successfully, with pretreatment and simultaneous antihistamines. The anemia resolved after 10 weeks. Iron dextran has sometimes been administered to patients who had previous anaphylactoid reactions due to pretreatment corticosteroids, antihistamines, ephedrine, hapten inhibition, and desensitization [11,12]. There are reports of desensitization protocols with other drugs requiring previous [13,14] or simultaneous therapy [15,16,17] with antihistamine, corticosteroids, or both. However, we could only find 1 case of desensitization to oral iron salts [3]. In this case, the clinical reaction involved a maculopapular exanthema and only a 30-mg dose of elemental iron (equivalent to 100 mg of ferrous sulphate) was reached. It took the patient 9 months to overcome the anemia. Unlike our case, the eruption reappeared immediately after the SBPCOC and with a lower dose of iron [3]. This type of reaction could be dose-dependent, as is the case with other allergenic agents, such as caffeine [18]. This dose dependence, as well as patient age, severity of anemia, and progress of the disease over time should be considered when designing and implementing a desensitization protocol for iron allergy in anemic patients.

In summary, we present a patient with iron-deficiency anemia and repeated iron salt anaphylaxis caused by a possible IgE-mediated immediate hypersensitivity mechanism and reproduced by different iron salts. Oral tolerance to ferrous sulphate was achieved with antihistamine treatment and a complete remission of the anemia was obtained.

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Manuel de Barrio Fernández

Servicio de Alergia
Hospital General Universitario "Gregorio Marañón"
Dr. Esquerdo, 46
28007 Madrid, Spain
E-mail: mdebarriof@hotmail.com

