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# Oral iron cutaneous adverse reaction and successful desensitization

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**Background:** The oral administering of iron preparations sometimes produces adverse gastrointestinal effects. In contrast, cutaneous reactions are extremely rare.

**Objective:** We report a patient with several episodes of generalized pruritus and erythematous maculopapular eruption after receiving oral compounds of iron and on whom desensitization with oral iron was attempted.

**Methods:** We studied a female with microcytic anemia due to gynecologic blood loss who presented several episodes of cutaneous eruption after receiving oral compounds of iron. Skin prick-test and two simple-blind, placebo-controlled oral challenges were performed with various iron compounds, and finally desensitization with oral iron was carried out.

**Results:** Skin prick-test and patch-test with iron preparations were negative. Two simple-blind, placebo-controlled oral challenges were performed and the patient began experiencing similar cutaneous symptoms. We started a slow desensitization protocol using increasing doses until the target amount of the drug was tolerated without adverse effects. The chronic administration of oral iron therapy once a day for 9 months sustained the desensitized state and the anemia disappeared.

**Conclusion:** We present methods to effectively manage iron supply for a microcytic anemia patient with cutaneous reactions due to oral iron compounds, to avoid repeated transfusions, slow desensitization with oral iron was successfully attempted.

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## INTRODUCTION

Oral iron therapy is frequently required for the treatment of iron deficiency anemia and is generally well tolerated. The most common adverse reactions are gastrointestinal effects.<sup>1</sup> Skin manifestations are extremely rare. In the reviewed literature, there have been only a few reported cases of adverse reactions due to iron therapy, and these reactions were likely due to treatment with iron dextran.<sup>2–4</sup> The following is a case in which a desensitization protocol was used for the administration of oral iron to a patient with a history of cutaneous reaction after starting oral iron therapy.

## CASE REPORT

A 40-year-old female without any personal or familial history of atrophy presented an iron deficiency anemia due to gynecologic blood loss. She was treated for weakness, palpitations, and lassitude. She underwent 3 months of oral iron therapy without any adverse reaction. Nine months after completing the treatment, she complained of being lightheaded upon sitting from a supine position. Laboratory data included a hemoglobin value of 9.1 g/dL, hematocrit value of 28.2%, mean cell volume of 71.6 fL, and mean cell hemoglobin value of 23.5 pg./cell. Two hours after starting treatment with oral iron therapy (Fero Gradumet®: 525 mg of dried ferrous sulfate, this is equivalent to 105 mg of elemental iron, Fe<sup>3+</sup>) she had an episode of generalized pruritus and erythematous maculopapular eruption on her trunk, forearms, and legs. The oral iron was discontinued and her

symptoms resolved in a day following treatment with, dexchlorfeniramine 5 mg IM. One week later her physician again administered iron (Ferrocure®: Ferrous proteinsuccinilate 800 mg, is equivalent to 40 mg Fe<sup>3+</sup>) causing a similar immediate reaction and she was treated with antihistamines immediately. Approximately 2 months later the patient was admitted to our allergy unit and the possible risks of the procedures were explained to the patient and her written informed consent was obtained prior to the study.

The skin prick-test was performed with serial 10-fold dilutions of ferrous proteinsuccinilate (Cicsa Schering, Madrid, Spain) in sterile diluent, starting with a 1:10,000 dilution, reaching a maximum concentration of 50 mg/mL (as is). Histamine phosphate (10 mg/mL) was used as positive control and physiologic saline as negative control. The results were expressed in the measurements (mm) of the larger wheal diameter 15 minutes after puncture. A wheal  $\geq 3$  in the presence of a negative response to the saline control was considered positive. Our patient's skin prick tests to ferrous proteinsuccinilate were negative. Patch testing carried out with the European standard series, ferrous sulphate 5% petrolatum (pet), ferrous proteinsuccinilate 5% pet, lyophilized natural ferric protein 5% pet, ferrous sulfate 5% pet, pure iron powder (p.p) 5% pet, polyethyleneglycol, and propylene glycol were negative (reactions were recorded following to the ICDRG scoring system).

The patient was included in a previously established single-blind, placebo-controlled drug challenge (SBPCDC).<sup>5</sup> The dosing protocol for the SBPCDCs is summarized in Table 1. After a positive SBPCDC, the chal-

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Table 1. Drugs and Doses Used for Single-Blind Challenge

| Lactose | Ferrous Sulfate |         | Ferrous Proteinsuccinilate |        |
|---------|-----------------|---------|----------------------------|--------|
|         | Dose            |         | Dose                       |        |
|         | 20 mg           | 5 mg*   | 40 mg                      | 2 mg*  |
|         | 100 mg          | 25 mg*  | 200 mg                     | 10 mg* |
|         | 250 mg          | 50 mg*  | 400 mg                     | 20 mg* |
|         | 525 mg          | 105 mg* | 800 mg                     | 40 mg* |

\* Equivalent of elemental iron.

challenge procedure was interrupted. Each SBPCDC was carried out separately on different days, with at least 7-day intervals between each challenge. During the challenge procedure, blood pressure was monitored (15 minutes, 30 minutes, and every hour after administering each drug or placebo dose or at any time when other symptoms were reported by the patient). The placebos initially followed by the iron were administered in opaque gelatin capsules with 60-minute intervals between doses. Two single-blind-placebo-controlled oral challenge tests were performed with ferrous sulfate 100 mg and later with ferrous proteinsuccinilate 200 mg. Approximately 30 minutes after administering the drugs, the patient started experiencing a severe generalized pruritus and widespread erythematous maculopapular eruption. She was treated immediately (cetirizine, 10 mg and methylprednisolone, 125 mg) and 14 hours later the cutaneous reactions had disappeared and the treatment was interrupted.

To avoid repeated transfusions, oral iron therapy (as ferrous sulfate) was again attempted. Oral iron, 5 mg Fe<sup>3+</sup>, was given, followed by the administration of oral iron 10 mg Fe<sup>3+</sup> 2 hours later. Twenty-four hours later, 10 mg Fe<sup>3+</sup> was given and another 20 mg Fe<sup>3+</sup> was administered approximately 2 hours after that. The next day 30 mg Fe<sup>3+</sup> was given and 1 hour later the

patient experienced mild generalized pruritus and an erythematous eruption on her forearms. Because she presented only a few symptoms, she was not treated and 12 hours later the symptoms disappeared. Another 30 mg Fe<sup>3+</sup> was administered twenty four hours after the previous dose (Table 2). The patient had no further problem and was discharged from the hospital the following day. She continued oral iron therapy for 9 months (30 mg of elemental iron daily), and the anemia disappeared.

DISCUSSION

This case illustrates a situation where a known adverse agent must be given to an individual with a history of a cutaneous reaction to the agent. In this case, desensitization must be done before the offending agent is administered. Large doses of iron are necessary to relieve iron deficiency, but we could not give her a maximum daily oral dosage of 100 mg of elemental iron.<sup>6</sup> We found that 30 mg of elemental iron daily was adequate treatment for this patient although higher doses are usually desirable. We could not reach the maximum dose because her symptoms started when she was given a low dose. Further, the patient refused to stay longer in the hospital for proper treatment. Desensitization is a process in which a person with a history of an

adverse reaction to a stimulus is rendered progressively less responsive by using repetitive exposure.<sup>7</sup> Historically, desensitization has been used for IgE-mediated hypersensitivity reactions.<sup>8,9</sup> A number of investigators, however, have shown that modified desensitization protocols, using increasing doses, successfully prevent non-IgE-mediated drug reaction to various pharmacologic agents.<sup>10</sup> The pathogenesis of this case remains unknown, although a delayed hypersensitivity mechanisms seems improbable. The patch test was done before the oral challenge in order to rule out this type of immunologic reaction. The clinical morphology should be consistent with a delayed allergic reaction, that is, a maculopapular rather than the urticarial rash associated with type I reactions. In the literature there are several cases of other skin reactions to drug, in which the primary lesion is not a rash typical of delayed type hypersensitivity (eczematous eruption). Positive patch test in these settings indicate a role for delayed-type hypersensitivity in these reactions<sup>11,12</sup>; however, in this case, our patient's patch tests were negative. Delayed hypersensitivity reaction to iron occurs within 4 to 48 hours after administering the drug and can last for 3 to 7 days. No such effects occurred in our patient.

The exact mechanism by which iron produces a cutaneous reaction is unknown. It may be due to hypersensitivity IgE mediated, although it also may be due to the release of cellular histamine from peripheral blood basophils or cutaneous mast cells<sup>2-4</sup> which is presumed to be the mechanism for severe reaction with radiocontrast media.<sup>13,14</sup>

The reaction could not have been to an additive because only the iron was common to the two drugs that produced the symptoms. The additives and preservatives were different for each drug. Although skin test does not confirm that this patient was sensitive to the iron, the history is suggested of sensitivity.

Table 2. Regimen Used to Give Elemental Iron as Ferrous Sulphate

|                | Day 1 | Day 2 | Day 3 | Day 4 |
|----------------|-------|-------|-------|-------|
| Elemental iron | 5 mg  | 10 mg | 30 mg | 30 mg |
|                | 10 mg | 20 mg |       |       |

Interval of increasing dosage in the same day: 2 hours.

In the literature review, there have been only a few reported studies of generalized cutaneous reaction to iron, all likely to have been due to the administration of iron dextran.<sup>2-4</sup> Our results confirm prior reports of the literature review on adverse reaction to oral iron.

We describe a rare case, which, after treating a iron deficient anemia with oral iron, caused a sudden eruption. By means of this paper we want to call attention to the fact that iron is frequently used and new cases of adverse reactions to this compound are likely to occur. This desensitization protocol enabled the patient to tolerate the administration of oral iron for 9 months, totaling 30 mg Fe<sup>3+</sup> per day. Because IgE antibodies to iron are exceedingly rare and slow increases in dosage may prevent important hypersensitivity reactions, we chose not to use a rapid desensitization protocol. In this patient with an adverse reaction to iron, the slow protocol desensitization allowed safe administration of oral iron.

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