

## Delayed Hypersensitivity Reaction to Iron Salts: From Diagnosis to Desensitization

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J Invest Allergol Clin Immunol 2022; Vol. 32(6): 496-498  
doi: 10.18176/jiaci.0789

**Key words:** Iron deficiency anemia. Delayed hypersensitivity. Desensitization. Lymphocyte transformation test. Diagnosis.

**Palabras clave:** Anemia ferropénica. Hipersensibilidad retardada. Desensibilización. Test de transformación linfocitaria. Diagnóstico.

Iron deficiency anemia (IDA) is a global public health problem because of its association with malnutrition and multiple medical conditions and the fact that it severely compromises the quality of life of affected patients [1]. IDA is highly prevalent in women of reproductive age, reaching 32.8% worldwide [2].

Iron treatment is considered a safe procedure, although adverse events, while rare, do occur. Cases of severe allergic reactions following iron administration have been reported [1-3]; of these, 25% result from iron hypersensitivity. One in every 5 million doses of intravenous iron administered is estimated to produce allergic reactions, most of which are immediate, with a mortality rate in the USA of 3 deaths per year [1].

A 48-year-old woman who had undergone gastric bypass for morbid obesity developed IDA with hemoglobin levels of 8.1 g/dL, transferrin saturation of 4.3%, ferritin of 12.62 ng/mL, blood iron levels of 16 µg/dL, and trace element deficiency (minerals and vitamins) associated with malnutrition syndrome. She was referred from the endocrinology and nutrition department. The endocrinologist initially treated IDA with oral therapy, although the patient began to vomit immediately after taking it. Therapy was then administered intravenously owing to the digestive symptoms and the lack of iron absorption resulting from the bypass.

The patient developed fever and asthenia 24 hours after administration of the first infusion of intravenous iron

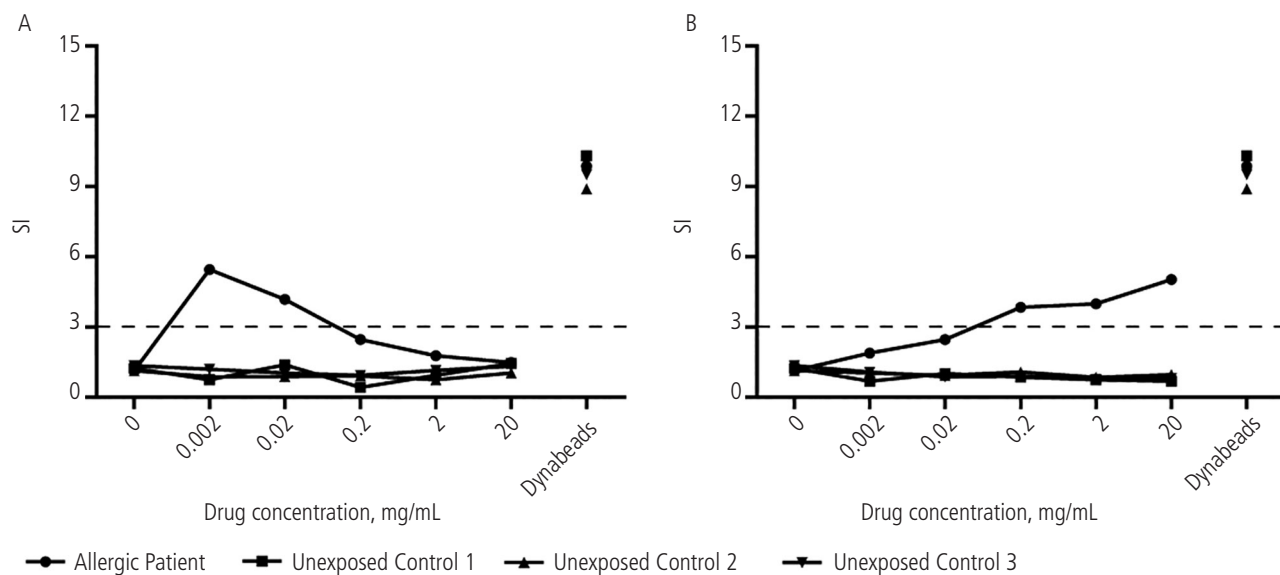
carboxymaltose. The symptoms subsided in 4 days without medication.

The patient was referred to the allergy department. A skin prick test (SPT) with iron carboxymaltose was performed 8 months after the reaction, and immediate and delayed readings (96 hours) yielded negative results. Intradermal testing was not performed because of the high risk of residual skin lesions. The referring physicians confirmed that iron carboxymaltose was mandatory because of malnutrition and intolerance to oral iron therapy. We assessed the management risks, and the patient signed the informed consent document. After assessment of risk, a drug provocation test (DPT) was performed with iron carboxymaltose, and no immediate reactions were reported. Three days later, the patient developed fever, nausea, diarrhea, and myalgia. She was prescribed oral prednisone (30 mg), cetirizine (10 mg), and paracetamol (1000 mg), and her symptoms resolved after 24 hours. Administration of iron carboxymaltose was contraindicated. Given the worsening of the IDA and the need for iron therapy, we decided to seek an alternative with iron sucrose. SPT with iron sucrose and immediate and delayed readings yielded negative results. DPT with iron sucrose was performed. Four hours after administration, the patient developed fever and generalized arthralgia.

In an attempt to determine the mechanism underlying this reaction, we performed a lymphocyte transformation test (LTT) with iron carboxymaltose and iron sucrose 2 months later. Peripheral blood mononuclear cells were isolated from whole blood using LymphoPrep gradient centrifugation. Briefly, 200 µL of cell suspensions (106 cells/mL) in AIM V Medium was added to each culture-plate well and stimulated with iron carboxymaltose and iron sucrose (20 µg/µL, 2 µg/µL, 0.2 µg/µL, 0.02 µg/µL, and 0.002 µg/µL). Dynabeads (Thermo Fisher Scientific; CD3/CD28 [1 µL/well]) were used as a positive control. Nonstimulated cells were used as a negative control. Cultures were performed in triplicate and incubated for 4 days at 37°C in an atmosphere of 5% CO<sub>2</sub>/95% air. On day 4, the culture plates were centrifuged and 100 µL of each well was replaced by fresh AIM-V medium containing 10 µCi of 3H-thymidine (3H). On day 6, cells were harvested using a vacuum manifold, and incorporation of radioactivity into DNA was measured using a liquid scintillation counter. The result is expressed as the stimulation index (SI), which is the relationship between the mean of triplicate dpm of the drug-stimulated cultures and the mean of triplicate dpm of the negative controls.

An SI of 2 to 3 is generally considered weakly positive. SI ≥3 was considered a positive response in our evaluation [4-6]. The reading was positive at a concentration of 0.02 µg/µL and 0.002 µg/µL of iron sucrose and 20 µg/µL, 2 µg/µL, and 0.2 µg/µL of iron carboxymaltose. An LTT with iron sucrose and iron carboxymaltose in 3 healthy controls revealed no proliferative responses (Figure). Since the patient was in need of intravenous iron treatment, rapid drug desensitization [7] was performed, with no breakthrough or delayed reactions (See Supplementary table).

Most reported hypersensitivity reactions (HSRs) to iron salts are immediate, and 1 in 200 000 patients treated with high-molecular-weight iron dextran experienced



**Figure.** Cell stimulation index according to drug concentration. A, Lymphocyte transformation test results for iron sucrose. B, Lymphocyte transformation test results for iron carboxymaltose. The test is considered positive when the SI is greater than 3 and, controls showed no proliferative responses in the lymphocyte transformation test with the drug. SI indicates stimulation index.

anaphylaxis. Many of the patients with an HSR to an iron salt preparation tolerated a different preparation in a rechallenge. Delayed reactions are rare, with only 11 cases reported [8]. Tolerance to an alternative iron formulation was achieved by rechallenge in 2 of the 11 patients. These cases were descriptive, with no allergy work-up. In the present case, the patient experienced a delayed reaction to iron carboxymaltose. Skin tests were negative in the late reading, and diagnosis was confirmed by means of a DPT. The patient presented another delayed reaction during rechallenge with iron sucrose. In cases of confirmed HSR where the patient must take a specific treatment, desensitization is an effective and safe alternative. In the present case, the patient tolerated desensitization to iron sucrose with no breakthrough or late reactions. LTT is currently the most frequently used test for the diagnosis of T cell–mediated hypersensitivity, especially in delayed hypersensitivity reactions to  $\beta$ -lactams and anticonvulsants [4]. To our knowledge, LTT has not been used in the diagnosis of HSR to iron salts. Here, we demonstrate that LTT could prove useful for elucidating the mechanism underlying delayed HSR to iron salts. Nevertheless, further research is needed to evaluate the role of LTT in the diagnosis of this reaction.

To our knowledge, this is the first case of type IV HSR to iron carboxymaltose and iron sucrose to be confirmed with positive DPT and LTT and successfully managed with desensitization. This case shows the LTT to be a promising new tool for the diagnosis of T cell–mediated HSR to iron preparations.

#### Funding

The authors declare that no funding was received for the present study.

#### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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■ *Manuscript received November 17, 2021; accepted for publication February 2, 2022.*

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