

A case report with hypersensitivity to ferrous but tolerance of ferric iron salts

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Clinical Implications

- Oral iron salts (OIS) are seldom responsible for hypersensitivity reactions. The pattern of cross-reactivity to OIS remains unclear in the literature. The presented case showed that ferric forms of OIS can be tolerated when there was sensitization to ferrous forms of OIS.

TO THE EDITOR:

Oral iron salts (OIS) are commonly used for iron deficiency. Adverse reactions to OIS, especially gastrointestinal side effects, are common.¹ In contrast to intravenous iron preparations, allergic reactions to OIS are rarely reported. In the literature, a small number of cases with hypersensitivity to only ferrous or to both ferrous and ferric forms were reported.²⁻⁵ Most of the previous reported cases are based on desensitization procedures instead of tolerance assessments.²⁻⁴

It is important to be confident about the absence of any alternative drug before attempting desensitization, which has intrinsic risks and complications.

We report here a child who had type I hypersensitivity to 2 separate forms of ferrous OIS. But the child was found to be able to tolerate ferric OIS. Hypersensitivity and tolerance to OIS were determined by skin prick/intradermal (ID) and oral provocation tests (OPTs).

A 42-month-old boy who had suffered from weakness and lack of appetite was diagnosed as having iron deficiency anemia. Oral iron replacement was initiated by the hematology department with oral ferrous (II) glycine sulfate. Between the 18th and 20th day of therapy, his mother complained of several pruriginous papules on his trunk that generally developed within 2 hours of ferrous (II) glycine sulfate intake. He was referred to the pediatric allergy department due to a possible allergic reaction. He had been followed up with recurrent wheezing episodes since his first birthday in the pediatric allergy department and used inhaled low-dose fluticasone dipropionate regularly. He had atopic sensitization to house dust mites. Results of skin prick test with undiluted ferrous (II) glycine sulfate and ID tests with 1:1000 and 1:100 dilutions of the drug were negative. The result of the ID test with a 1:10 dilution of ferrous (II) glycine sulfate was found positive (Figure 1). Because we do not know what concentration of OIS causes irritation during skin testing, the positive ID test response at 1:10 dilution required further validation. An OPT was performed with ferrous (II) glycine sulfate. An intravenous line was placed and vital signs were recorded before the OPTs and each dose increase. Fifty minutes after the second graded dose (60 mg), he experienced 5 to 6 urticarial eruptions on his neck and thorax. The patient subsequently underwent an OPT with ferrous (II) fumarate after the skin test and the ID test showed negative response. He developed 3 to 4

urticarial lesions 45 minutes after the second dose (40 mg). One week later, a third OPT with ferric (III) polymaltose complex as an alternative OIS was conducted after negative skin prick test and ID test results. The OPT with 140 mg cumulative dose of ferric (III) polymaltose complex revealed no reaction (for details on skin testing and OPT procedures, see this article's Online Repository at www.jaci-inpractice.org). He has been using the ferric form for about 3 months without any reaction.

To our knowledge, this is the first case in the literature that had confirmed hypersensitivity to ferrous (II) glycine sulfate and ferrous (II) fumarate, but tolerated ferric (III) polymaltose complex.

OIS are seldom responsible for hypersensitivity reactions. There have been a few cases in the literature reporting reactions such as maculopapular³ or pustular eruptions,⁶ vasculitis,⁷ photodermatitis,⁸ urticaria and angioedema,⁴ and anaphylaxis.²⁻⁵ In most of those reports, either ferrous or ferric forms of iron preparations are responsible for the reactions.

There are few reports in the literature describing desensitization procedures to OIS. In some of those reports, patients were found to be sensitive to both ferrous and ferric forms of OIS. But in others, tolerance or sensitivity to other OIS except the culprit drug was not investigated and desensitization was accomplished without the evaluation of cross-reactivity.²⁻⁵ Those patients' clinical conditions may have required rapid solutions such that there was not enough time for broad clinical investigations. In our opinion, investigations about cross-reactivity/tolerance to alternative OIS have to be performed whenever the patient's clinical condition is feasible and the clinical reaction is not severe.

The pattern of cross-reactivity to OIS remains unclear in the literature. The presented case showed that ferric forms of OIS can be tolerated when there was sensitization to ferrous forms of OIS. Although it is difficult to extend conclusions from just 1 case, investigation of cross-reactivity to OIS may be important when offering patients alternative treatments, especially when the reaction is not severe and there is time to consider alternatives. Therefore, it is necessary to individualize how to face a case of hypersensitivity to iron salts.

The type (urticaria) and timing of allergic reaction (within 1 hour) after the last intake correspond to type I hypersensitivity reactions. IgE-mediated hypersensitivity was also possibly suggested by the positive ID test result, though this interpretation should be made with great caution given the unknown irritating concentration of OIS for skin test. Iron salts have low molecular weights and bind to high molecular weight molecules to be recognized by the immune system.⁹ Ferric (III) iron salts are the most stable form of the molecule.¹⁰ The stability of the molecule may result in less binding to other macromolecules and therefore less allergenicity. In addition, ferric forms of iron salts are less absorbable than the ferrous forms, decreasing the available molecule in the blood to be able to cause an allergic reaction. This may also contribute to the scarcity of allergic reactions reported with ferric relative to ferrous iron salts in the literature.

Cross-reactivity among ferrous iron preparations, namely, ferrous sulfate, ferrous ascorbate, and ferrous lactate, has been reported.⁹ Based on our case, ferrous fumarate may also be added to those groups of cross-reactivity.

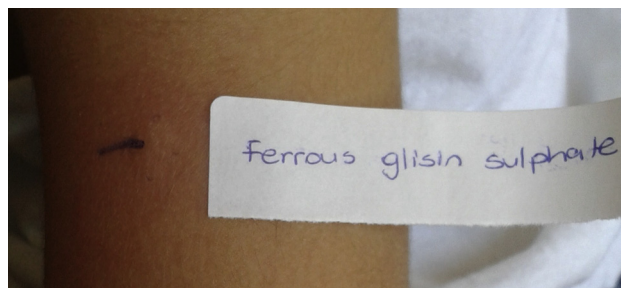


FIGURE 1. ID test with a 1:10 dilution of ferrous (II) glycine sulfate showed a positive response as seen in the picture (7-mm wheal/6-mm flare).

Another reason for the urticarial reactions in our patient may have been related to the excipients that were present in the commercial syrup formulations. This seems less likely because ferrous (II) glycine sulfate and ferrous (II) fumarate formulations each contained several excipients that were distinct from each other.

In summary, OIS may cause hypersensitivity reactions that seem to IgE mediated. There has been some degree of cross-reactivity documented among ferrous OIS. Ferric iron salts may be an alternative for some patients found to be intolerant of ferrous iron salts. Therefore, an individualized assessment plan for patients with hypersensitivity to OIS would be appropriate.

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Skin Prick/intradermal tests with oral iron salts

For skin prick tests (SPTs) with ferrous (II) glycine sulphate, ferrous (II) fumarate and ferric (III) polymaltose complex, undiluted commercially available syrup formulations were used (Ferrous glycine sulphate: Ferro Sanol B® syrup, Adeka, Istanbul-Turkey; Ferrous fumarate: Ferrozinc® syrup, Bikar, Istanbul-Turkey; Ferric polymaltose complex: Ferrifer® 40 oral solution, Berko, Istanbul-Turkey). Isotonic saline was used to make intradermal (ID) solutions. ID tests were performed at 1:1000, 1:100 and 1:10 dilutions of ferrous glycine sulphate, ferrous fumarate and ferric polymaltose complex.

SPTs with undiluted commercially available forms were negative for oral iron formulations. ID tests with 1:1000, 1:100 and 1:10 dilutions of three oral iron salts were also negative except ID test with 1:10 dilution of ferrous (II) glycine sulphate [Figure 1]. IDT was considered positive if the mean wheal diameter is increased ≥ 3 mm than the negative control with a surrounding erythema after twenty minutes of application. We

did not perform ID skin testing in duplicates. As we do not know irritating concentration of oral iron salts for skin testing, the positive test response with 1:10 dilution of ferrous (II) glycine sulphate and the negative test response with ferrous fumarate required further validation. Therefore, we performed OPTs.

Oral provocation tests with oral iron salts

Oral provocation testing was performed with two to three graded doses and were calculated as elemental iron equivalence. Incremental doses were administered at intervals of 60 minutes up to the planned therapeutic dose. The incremental doses were as follows: ferrous glycine sulphate (30 mg-60 mg), ferrous fumarate (20 mg-40 mg) and ferric polymaltose complex (20 mg-40 mg-80 mg). The patient was kept under strict medical observation for up to 2 hours after completing the test in case of a negative test. In the case of a positive reaction, the oral challenge was stopped and the patient was treated symptomatically and was kept under medical observation until all symptoms were completely resolved.

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