
Severe Anaphylactic Reaction to Ferric Carboxymaltose With Positive Skin and Basophil Activation Tests

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Intravenous iron therapies (IVITs) are usually prescribed to prevent or treat iron deficiency anemia in patients with chronic kidney disease, pre- or postoperative situations, and intestinal absorption disorders when oral iron drugs are inappropriate, ineffective, or not tolerated [1-3]. Life-threatening hypersensitivity reactions (HSRs) have been reported with iron encased in dextran-derived preparations (DDPs). These reactions are probably due to IgG and IgM antibodies to dextran [4].

Previous studies have shown that current parenteral iron products have a better safety record, although HSRs still occur [5]. An analysis of 5247 patients treated with various IVITs did not show a significant difference in the prevalence of moderate or severe HSRs between patients receiving DDPs or new preparations containing ferric carboxymaltose (FCM) or iron sucrose (IS) [5].

We report a case of severe anaphylaxis occurring during the administration of FCM.

A 35-year-old pregnant woman was referred to the emergency department for spontaneous preterm rupture of membranes and onset of labor. Cesarean section was performed because the patient was at week 37+1 of gestation and was expecting twins. Spinal anesthesia was initiated at 12:07 PM, when she received sufentanil citrate, bupivacaine, morphine hydrochloride, and ephedrine, followed by cefuroxime at 12:19 PM, oxytocin at 12:25 PM, and ropivacaine at 12:46 PM. She developed a postpartum hemorrhage with bleeding volume requiring the administration of sulprostone at 1:00 PM and was transferred to the postoperative monitoring room at 1:05 PM. Hemodynamic monitoring was performed throughout the

surgical procedure and during the immediate postoperative phase. Intravenous iron administration was started at 1:30 PM with 1000 mg of FCM. Fifteen minutes later, the patient developed faintness, bilateral loss of vision, and hypotension (50/30 mmHg) followed by diffuse urticaria and acute bronchospasm. The FCM infusion was stopped, and the patient was treated with high-flow oxygen and IV epinephrine (cumulative dose 800 µg). She received 2500 mL of crystalloid fluids, continuous IV norepinephrine, IV methylprednisolone, and nebulized salbutamol, with complete resolution of allergic symptoms 8 hours later.

Tryptase measured 30 minutes and 2 hours after the start of the reaction reached 73 and 111 µg/L before gradually decreasing 24 hours and 45 weeks later to 8.31 and 5.89 µg/L, respectively.

Her past medical history was remarkable for asthma with no current medication, although she had never experienced allergy, including drug allergy. To our knowledge, she had never previously received oral or IV iron therapy.

Skin testing was performed 45 weeks later according to the recommendations of the European Academy of Allergy and Clinical Immunology [6].

IgE testing with latex and chlorhexidine was negative. Skin prick tests (SPTs) and intradermal tests (IDTs) with chlorhexidine and ropivacaine were negative, and IDTs with sulprostone were negative up to 2.5 µg/mL.

SPTs and IDTs were performed with FCM and IS up to 50 and 20 mg/mL, respectively. SPTs to both IVITs were negative. IDT to FCM was strongly positive at 0.05 mg/mL. IDTs to IS were negative at 0.02 and 0.2 mg/L and doubtful at 2 mg/mL (see Table 1 in online appendix). SPTs were negative for ferrous fumarate and ferric sodium EDTA. There was no residual pigmentation due to the iron products tested.

A basophil activation test (BAT) with CD63 expression was positive for FCM and negative for IS (Figure, A, left panel). Yellow jacket venom was used as a negative control allergen (Figure, A, right panel). To exclude the possibility of FCM or IS acting as a nonspecific basophil activator, basophils from another exposed patient (#4) and unexposed controls (#1-2-3) were analyzed in the presence of these drugs (Figure, B).

The patient gave her informed consent for provocation tests. Challenges with oral ferrous fumarate and IV IS were performed without symptoms up to the cumulative therapeutic doses of 66 and 101 mg of elemental iron, respectively.

Excluding high-molecular-weight iron dextran, the risk of anaphylaxis (serious adverse effects [AEs]) associated with IVIT is estimated at less than 1 in 200 000 [1,2,5]. In 2013, the European Medicines Agency (EMA) published a report of their 2-year investigation of adverse drug reactions to all IVITs

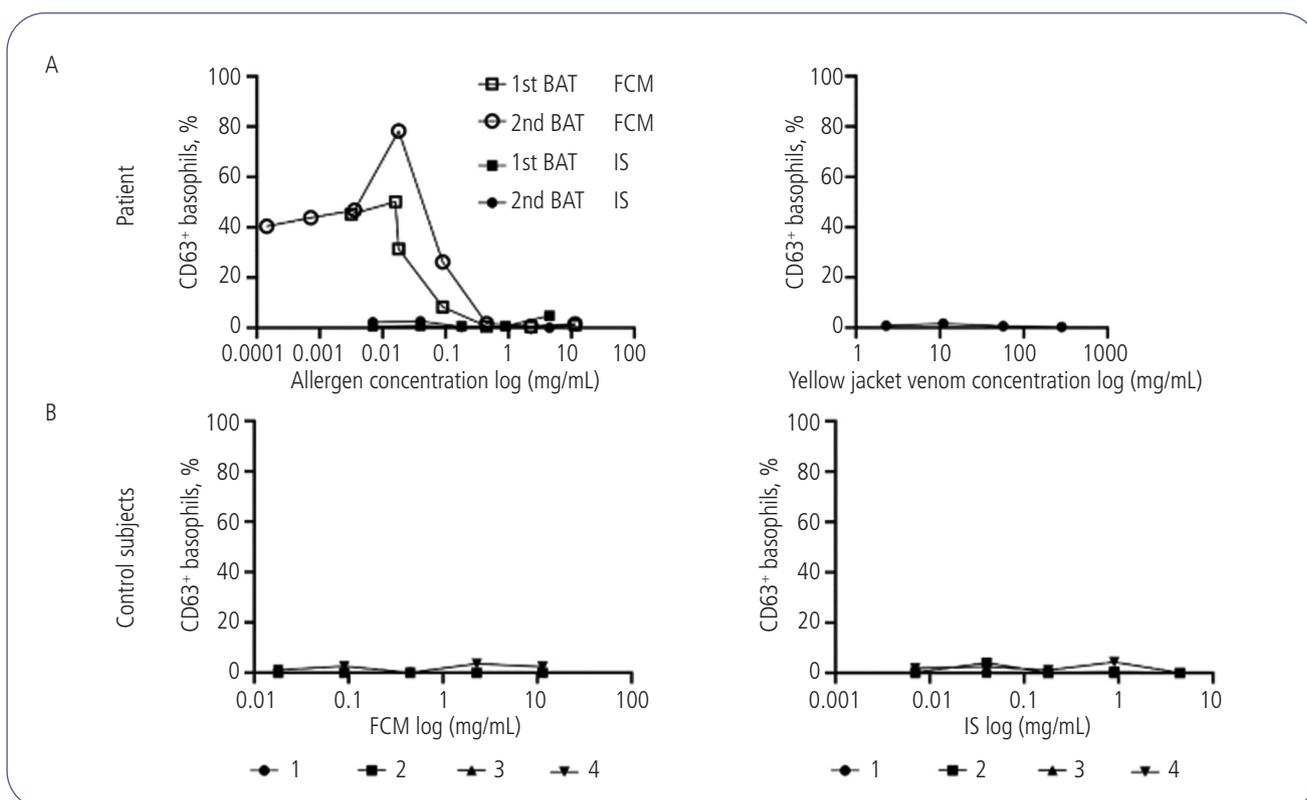


Figure. Dose-response curve for basophil activation with increasing concentrations of IS or FCM. Results are expressed as a percentage of CD63-positive basophils. BATs were performed using flow cytometry with a Flow CAST assay (Bühlmann). A, Patient BATs with IS and FCM (left panel) or with yellow jacket venom (right panel). B, Control BATs with FCM (left panel) or IS (right panel). Controls #1, 2, and 3: not exposed to FCM and IS. Control #4: exposed to FCM. IS indicates iron sucrose; FCM, ferric carboxymaltose; BAT, basophil activation test.

available in Europe. A total of 236 cases of hypersensitivity to FCM were identified in a population of 393 160 patient-years. This corresponds to a hypersensitivity event frequency rate of 0.060% [3].

The incidence and severity of HSRs seem to be increased by a fast iron infusion rate, previous AEs to IVIT or other drugs, a history of severe atopy, and systemic mastocytosis. Pre-existing severe respiratory or cardiac disease, older age, and use of β -blockers or ACE inhibitors may worsen the outcome of HSR [1,7].

It should be noted that HSRs have been reported for patients who had previously received multiple doses of parenteral iron without AE. According to the EMA recommendation [3], IVIT should be contraindicated in patients with a history of reaction to other parenteral iron-containing products or, in the case of HSR, to the active substance or any of the excipients. In Europe, the administration of IVIT does not require a previous testing dose. Thus, in selected patients with identified risk factors for HSR, a lower dose may be considered based on expert opinion [3].

While most adverse reactions to iron treatments are probably not IgE-mediated, the underlying mechanisms remain unclear [7].

IgE- and IgG-mediated anaphylaxis to previous IVITs have already been suspected, especially for dextran iron. However, Rampton et al [7] found no data to support the concept that IgE-mediated hypersensitivity commonly accounts for reactions to current parenteral formulations. Today, IgG-mediated anaphylaxis to dextran is the only mechanism that remains undisputed.

The reactions to IVIT might be explained by complement activation-related pseudoallergy (CARPA). The activation of complement by anaphylatoxins C5a and C3a leads to flushing via vasodilation, urticaria, and wheezing [1,2,4,5]. Hempel et al [8] found that FCM has complement-activating capacities in vitro and somehow ex vivo. Therefore, HSRs to this drug could be CARPA-mediated.

Drug-induced anaphylaxis has been attributed to mast cell activation via mas-related G protein coupled receptor X2 (MRGPRX2), which has not been involved in hypersensitivity to IVIT to date.

Carrón-Herrero et al [9] reported T cell-mediated hypersensitivity to iron salts with positive lymphocyte transformation test results for FCM and IS. The case involved a single observation of a man referred for fever, fatigue, and arthralgia after various IVITs. This mechanism is also involved in contact allergy to iron.

Morales Mateluna et al [10] explored 31 patients referred for suspected HSR to IVIT. FCM was involved in 19 cases (61.3%). Based on the Ring and Messmer scale, 7 patients were classified as grade II, 5 as grade III, and 4 as grade IV. SPTs with the undiluted suspected product and BAT were performed for 11 and 10 patients respectively. SPTs and BATs were negative for all patients tested.

FCM was definitively contraindicated in the case we report owing to severe anaphylaxis after infusion with positive IDT and BAT findings.

We report a case of anaphylaxis to FCM with positive BAT results only to the offending drug and positive IDT results with

nonirritating dilutions, strongly suggesting an IgE-mediated allergy, albeit without full confirmation. Thus, in contrast with previous authors who concluded that skin testing and BATs provided no additional information [10], we recommend that cases of severe anaphylaxis after IVIT be managed based on skin tests and BAT with the offending IVIT. A safe alternative IVIT should be sought.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentation

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