Severe anaphylactic reaction to ferric carboxymaltose with positive skin and basophil activation tests

Moreaux S[1,2], Hammoud R[1,2], Beauvillain C[3], Babin M[2], Husser Vidal S[4], Nicolie B[1], Morisset M[1]

[1]Allergy unit, Angers University Hospital
[2]Regional Pharmacovigilance Center, Angers University Hospital
[3]Univ Angers, Nantes Université, CHU Angers, Inserm, CNRS, CRCI[2]NA, SFR ICAT, F-49000 Angers France
[4]Anesthesiology & Critical Care Department, Angers University Hospital, France

Morisset Martine
CHU Angers
4, rue Larrey - 49100 France
martine.morisset@chu-angers.fr

doi: 10.18176/jiaci.0870

Intravenous iron therapies (IVIT) are usually prescribed to prevent or treat iron deficiency anemia, in chronic kidney disease patients, pre- or post-operative situations, or intestinal absorption disorders when oral iron drugs are inappropriate, ineffective or not tolerated [1-3]. Life threatening hypersensitivity reactions (HSRs) were reported with iron encased in dextran-derived preparations (DDP). 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, but HSRs still occur [5]. An analysis of 5247 patients treated with various IVIT did not show a significant difference in the prevalence of moderate or severe HSRs between patients receiving DDP or new preparations containing ferric carboxymaltose (FCM) or iron sucrose (IS) [5].

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

A 35-year-old pregnant woman was referred to the emergency unit for a spontaneous preterm rupture of membranes and onset of the labor. Due to a 37+1 gestation week twin pregnancy, a caesarian section was performed. A spinal anesthesia began at 12:07 p.m., when she received sufentanil citrate, bupivacaine, morphine hydrochloride, and ephedrine, followed by cefuroxime at 12:19 p.m., oxytocin at 12:25 p.m., and ropivacaine at 12:46 p.m. She presented with a postpartum hemorrhage with bleeding volume requiring the administration of sulprostone at 1:00 p.m. She was transferred to the postoperative monitoring room at 1:05 p.m. Hemodynamic monitoring was performed throughout the surgical procedure and during the immediate postoperative phase. Intravenous iron administration of 1000 mg of FCM started at 1:30 pm and 15 minutes later, she presented with faintness, bilateral loss of vision, and hypotension (50/30 mmHg), followed by a diffuse urticaria and acute bronchospasm. FCM infusion was stopped, and the patient was treated with high flow oxygen and IV epinephrine (cumulated dose 800 µg). She received 2500 mL crystalloid filling, continuous IV norepinephrine, IV methylprednisolone and salbutamol nebulization, with a complete resolution of allergic symptoms 8 hours later.

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

Her past medical history was remarkable for asthma without any current medication, but she never suffered from allergy, including drug allergy. She had never previously received oral or IV iron therapy to our knowledge.

Skin testing was performed 45 weeks later according to the EAACI recommendations [6].

IgE to latex and chlorhexidine were negative. Skin prick tests (SPTs) and intradermal tests (IDTs) to chlorhexidine and ropivacaine were negative and IDTs to 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 IVIT 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 appendix online). SPTs were negative for ferrous fumarate and ferric sodium EDTA. There was no residual pigmentation due to the iron products tested.

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

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

Excluding high molecular weight iron dextrans, the risk of anaphylaxis (serious adverse event -AE) associated with IVIT is estimated at less than 1 in 200,000 [1, 2, 5]. In 2013, the

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European Medicines Agency (EMA) published a report of their 2-year investigation of the adverse drug reactions to all IVIT available in Europe. A total of 236 hypersensitivity cases were identified with FCM, which occurred out of a population of 393,160 patient-years. This corresponds to a hypersensitivity event frequency rate of 0.060% [3].

A fast iron infusion rate, previous AE to IVIT or other drugs, history of severe atopy and systemic mastocytosis, appear to increase the incidence and severity of HSRs. Pre-existing severe respiratory or cardiac disease, old age and use of beta-blockers or ACE inhibitors may worsen the outcome of a HSR [1, 7].

It should be noted that HSRs have been reported for patients who had previously received multiple parenteral iron administrations without AE. According to the EMA recommendation [3], IVIT should be contraindicated in patient with a history of reaction with other parenteral iron containing product, or in 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].

Most of adverse reactions to iron treatments are probably not IgE-mediated responses, but underlying mechanisms remain unclear [7].
IgE- and IgG-mediated anaphylaxis to previous IVIT have already been suspected, especially for dextran iron, but Rampton and al. found no data to support the concept that IgE-mediated hypersensitivity commonly accounts for reactions to current parenteral formulations [7]. Today, IgG-mediated anaphylaxis to dextrans is the only mechanism that remains undisputed.
Complement activation related pseudoallergy (CARPA) could be a possible explanation for reactions to IVIT. The activation of complement by anaphylatoxins C5a and C3a production leads to flushing via vasodilation, urticaria, wheezing [1, 2, 4, 5]. Hempel and al. found that FCM have complement-activating capacities in-vitro and somehow ex-vivo, so HSRs to this drug could be CARPA-mediated [8].

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

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

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

Concerning our patient, due to a severe anaphylaxis after infusion with positive IDT and BAT, FCM was definitively contra-indicated.

We report a case of anaphylaxis to FCM with positive BAT only to the offending drug and positive IDT with non-irritating dilution strongly suggesting an IgE-mediated allergy without being able to fully confirm it. Thus, in contradiction with previous authors who concluded that skin testing and BATs provided no additional information [10], in case of severe anaphylaxis to IVIT skin tests and BAT to the offending IVIT and alternative therapy should be considered to propose a safe alternative IVIT.

Key words: Anaphylaxis. Drug hypersensitivity. Iron compounds. Basophil Activation Test. Intradermal tests.

Palabras clave: Anafilaxia. Hipersensibilidad a medicamentos. Compuestos del hierro. Test de activación de basófilos. Test intradérmicos.

doi: 10.18176/jiaci.0870

Part of this work was presented (*after the first submission to the JIACI*) as a poster in French at the Congrès Francophone d'Allergologie 2022, and as an e-poster in English during the EAACI Congress 2022.

Conflicts of Interest

The authors declare that they have no conflicts of interest. There were no funding sources.

doi: 10.18176/jiaci.0870

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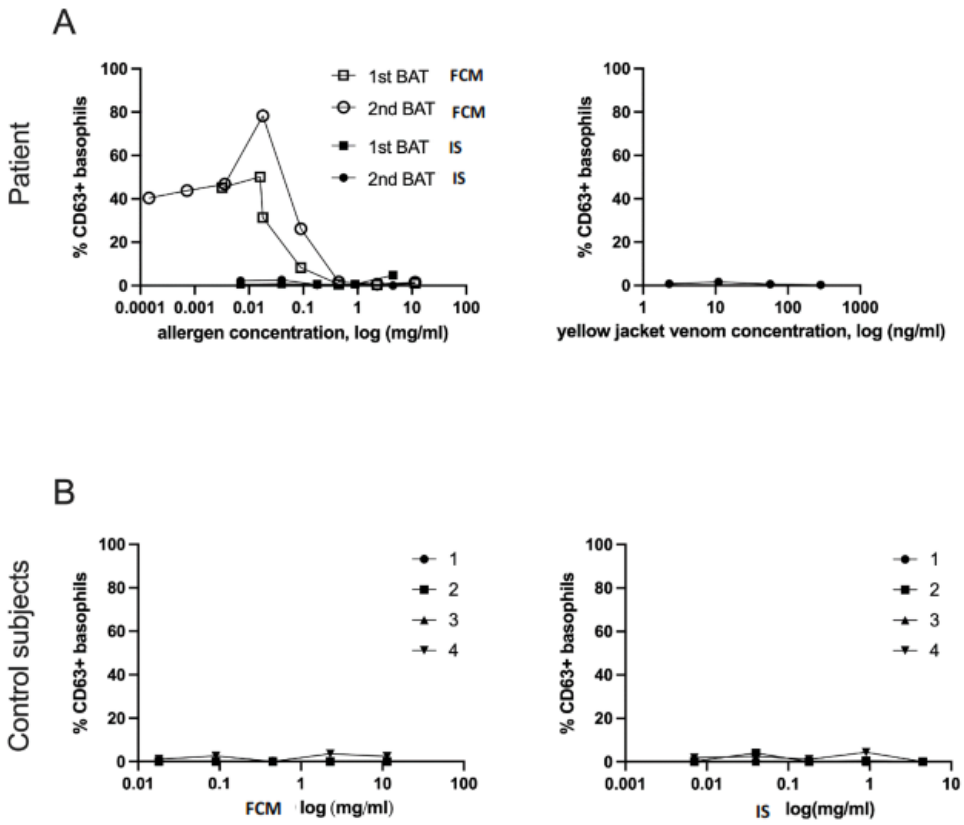
doi: 10.18176/jiaci.0870

Figure 1. Dose-response curve of basophil activation with increasing concentrations of IS or FCM of the patient. Results are expressed in % of CD63 positive basophils. BATs were done with a Flow CAST® assay (Bühlman) by flow cytometry. (A) Patient BATs with IS and FCM (left panel) or with yellow jacket venom (right panel). (B) Control subjects BATs with FCM (left panel) or IS (right panel).
Control subjects #1-2-3: subjects unexposed to FCM and IS.
Control subject #4: patient exposed to FCM.



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