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CASE REPORT

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Successful Rapid Drug Desensitization to Ferric Carboxymaltose in Four Patients

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ABSTRACT

An iron hypersensitivity reaction can develop during infusion. Here we present four cases of Rapid Drug Desensitization (RDD) as an option for the treatment of these patients. Urticaria appeared in the second hour of an IV iron sucrose infusion (ISI) performed 8 years previously in case 1 and drug provocation with IV ferric carboxymaltose was performed, but urticaria developed on the arm where the drug was administered immediately after infusing 60 cc. Case 2 developed tongue swelling and shortness of breath within minutes of the IV ISI. Case 3 developed shortness of breath within three minutes after the first dose of IV ISI. Case 4 with iron deficiency anemia reported swelling in the throat, lips and shortness of breath after taking an unknown oral iron therapy. On the 14th day of oral ferrous sulfate therapy, the patient presented with pruritus and skin eruptions occurring 2 hours after drug ingestion. Fifteen RDDs were successfully performed in these cases.

Keywords: Iron hypersensitivity, desensitization, ferric carboxymaltose, iron deficiency anemia

INTRODUCTION

Iron deficiency is a common health problem and treatment is generally based on iron supplements as oral iron salts (1). Although oral iron administration is generally well tolerated, adverse effects are frequently encountered and allergic reactions are rarely reported.

Treatment with IV iron clearly has an advantage over oral iron. The first IV iron product was high-molecular-weight iron dextran. Due to the elevated risk of anaphylactic reactions to dextran-containing IV preparations, new IV iron preparations were introduced into the market. Three new IV iron compounds, ferric carboxymaltose (FCM), iron isomaltoside, and ferumoxytol have recently been released for clinical use with a better safety profile. Hypersensitivity reactions (HSR) have now become less frequent; however, severe reactions may still occur (2).

Rapid drug desensitization (RDD) might be a method for patients with iron deficiency anemia (IDA) who have severe allergic reactions during parenteral iron therapy. Considering the rarity of RDD with IV iron, we present our experience with RDD to FCM in four patients. This study was approved by the institutional review board at Ankara University (24.09.2018, No: 15-1010-18).

CASE HISTORIES

Case 1

A 30-year-old female patient had IDA for 21 years, which was unresponsive to oral irons (Table I). The patient's history revealed generalized itching, redness, and swelling appearing in the second hour of an IV iron sucrose infusion which had been performed 8 years ago. FCM prick test and intradermal tests were negative. Drug provocation with IV FCM was performed, but a burning sensation, swelling, and urticarial plaques developed on the arm immediately after the 60 cc drug was infused.

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Case 2

A 75-year-old male patient had been diagnosed as having IDA 10 years ago due to colon cancer. The patient developed diarrhea and nausea 4 hours after taking the second dose of ferrous sulfate. He developed tongue swelling and shortness of breath within minutes of the IV iron sucrose infusion.

Case 3

A 35-year-old female patient had been diagnosed as having IDA 5 years ago. She had had nausea and vomiting 15 minutes after the first dose of an unknown oral iron tablet. The patient had developed shortness of breath within three minutes of administration of the first dose of IV iron sucrose infusion.

Case 4

A 23-year-old female patient with chronic IDA reported swelling in the throat, lips and face, hoarseness, and shortness of breath after taking an unknown oral iron tablet. On the 14th day of oral ferrous sulfate therapy, the patient presented with extensive pruritus, and erythematous punctate eruptions that had occurred 2 hours after drug ingestion. In addition, she had suffered urticarial plaques on the whole body and swelling of the throat and lips occurring 7 years ago after taking some non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics.

DESENSITIZATION PROTOCOL

After written consent was obtained, RDD was performed using FCM with a standard 12-step protocol developed for chemotherapeutic agents (3) (Table II). The patients were premedicated with H1 and H2 blockers, systemic steroids, and a leukotriene antagonist, and were desensitized by an experienced allergist using established protocols. As an experienced department in RDD, we provided one-to-one desensitization-trained nurse/patient care for each desensitization procedure. No breakthrough reactions were noted during or after the infusion.

DISCUSSION

We present four patients with iron hypersensitivity who were successfully desensitized with FCM via RDD. The protocol was effective because the patients' follow-up examinations demonstrated evidence of the success of the treatment (Table I).

Adverse reactions associated with iron therapy are very common and well defined (1). However, knowledge about HSR is limited because of the rarity of these reactions. Drug HSR due to iron therapy may occur immunologically (IgE-mediated or complement activation) or non-immunologically but the exact pathogenesis is still poorly understood because the clinical presentations in both reaction types are similar and the clinical manifestations alone are insufficient to understand the underlying mechanism (4). Considering the value of diagnostic tests in iron allergy, skin tests are not validated. In one retrospective study, none of 31 patients with mild-to-severe immediate-type reactions have shown positivity in skin prick tests (5). Although drug provocation testing can be performed to confirm the diagnosis, it is unsafe particularly in patients with a history of severe reactions. The results of the prick test using the undiluted FCM (25 mg/ml) and intradermal tests using serial dilutions (1/10, 1/100) were negative in patients #1 and #4. Patient #2 had been on oral steroids and patient #3 was on an anti-depressant drug; therefore, skin tests were performed but there was no reaction with histamine either.

Several risk factors for HSR to IV iron preparations have been defined (6). In our series, the second and third patient reacted to IV iron sucrose. Additionally, the

Table I. Hematologic data of the patients

Case	HB (g/dL) (N: 11. 7-15.5)		HTO (%) (N: 35-45)		MCV (fL) (N: 81-100)		MCH(pg/cell) (N: 27-34)		MCHC(g/dL) (N: 32-36)		Ferritin(u/L) (N: 11-306.8)		Iron(u/dL) (N: 60-180)	
	Pre-post RDD		Pre-post RDD		Pre-post RDD		Pre-post RDD		Pre-post RDD		Pre-post RDD		Pre-post RDD	
1	7.9	10.8	29.8	37.1	63.9	71.3	17	20.8	26.5	29.1	9.3	49.3	14	29
2	5.9	10.5	18.3	32.2	69.3	84.7	22.2	27.6	32.1	32.6	1.8	7.1	11	25
3	10.3	np	35	np	70.9	np	20.9	np	29.4	np	1.7	np	21	np
4	9.6	11.8	32.1	36.6	73	79.9	21.7	25.8	29.8	32.2	3.4	5.2	25	45

N: Normal, **np:** Not performed

Table II. Rapid desensitization protocol with IV ferric carboxymaltose (target dose: 500 mg)

Solution 1: 1/100 Solution 2: 1/10 Solution 3: 1/1					
Ferric carboxymaltose 500 mg/10 mL					
Step	**Solution**	**Rate (mL/hr)**	**Time (min)**	**Volume infused per step (mL)**	**Cumulative dose (mg)**
1	1	2.5	15	0.60	0,013
2	1	5	15	1.25	0,038
3	1	10	15	2.50	0,088
4	1	20	15	5.00	0.188
			Vital signs were monitored		
5	2	5	15	1.25	0.438
6	2	10	15	2.50	0.938
7	2	20	15	5.00	1, 938
8	2	40	15	10.0	3.938
			Vital signs were monitored		
9	3	10	15	2.50	8.888
10	3	20	15	5.00	18,788
11	3	40	15	10.0	38.588
12	3	60	186	232.50	500 mg

Premedication: 60 minutes before: methylprednisolone 40 mg IV, ranitidine 50 mg IV, cetirizine 10 mg PO, acetylsalicylic acid 300 mg PO, montelukast 10 mg, PO
PO: Per-oral, **IV:** Intravenous

second patient was old and the last patient had a history of antibiotic and NSAID HSR besides the immediate reactions to two oral iron preparations. FCM was chosen as the IV iron preparation by a hematologist because of its very low immunogenic potential. However, considering the potential for HSR, we performed desensitization to FCM in our patients instead of regular infusion.

Desensitization procedures allow patients to receive their necessary medication safely. However, reports with IV iron desensitization protocols are scarce in the literature. To date, a few IV iron desensitization protocols for IV iron dextran, iron sucrose, and FCM have been published. Three patients with HSR to IV iron dextran were successfully desensitized (7, 8). Later, Rodriguez-Jimenez et al reported a rapid desensitization protocol to IV iron sucrose in a patient who had generalized urticaria and facial angioedema after oral ferrous sulfate ingestion (9). The first case series of FCM desensitization in patients with prior anaphylaxis to other IV iron formulations was recently reported. The study group used a different desensitization protocol; a stock concentration of 2 mg/mL and then each dose was infused over 15-minute intervals at an increasing rate (10).

A standardized desensitization protocol for IV iron is not available in the literature. In these four patients with HSR to iron, we showed that the 3-bag, 12-step desensitization protocol, which has been used for several drugs including biologics and chemotherapeutics, worked well with no significant adverse effects. To our knowledge, this is the first report with this protocol. The protocol can be recommended in patients with HSR to iron with IDA who require iron replacement therapy.

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