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Case Report

Hypersensitivity reactions to intravenous ferric carboxymaltose in a patient with iron deficiency anemia: a rare case report

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ABSTRACT

Ferric carboxymaltose (FCM) is a non-dextran iron preparation recently approved in the United States for intravenous treatment of iron deficiency anemia (IDA) in adult patients with intolerance or poor response to oral iron therapy. Acute hypersensitivity reactions (HSRs) during iron infusions are very rare but can be life-threatening. Adverse events, including immune system disorders (0% in FCM) and skin disorders (7.3% in FCM), are less frequently observed with FCM. On treatment with FCM, the change in hemoglobin from baseline to the highest observed level is about 2.8g/dL. Treatment of IDA with FCM resulted in fewer hypersensitivity reactions. Here, authors report a case of a 23 years old female diagnosed for IDA presented with the picture of adverse drug reaction due to injection FCM given by the physician. The patient was managed with Antibiotics, Corticosteroids and Intravenous fluids and recovered well within 12 hours of admission from this adverse drug reaction. Since such cases have been rarely reported, authors are intended to notify about this potentially dangerous drug reaction due to FCM which is used extensively in the treatment of IDA. Hence management of iron infusions requires very careful and precise observation, and, in the event of an adverse reaction, prompt recognition and severity-related interventions by well-trained medical and nursing staff.

Keywords: Ferric carboxymaltose, Hypersensitivity reactions, Iron deficiency anemia

INTRODUCTION

Iron deficiency is the most common cause of anemia and typically results from impaired absorption of dietary iron, increased iron losses (e.g., menstruation, gastrointestinal bleeding), and increased utilization (e.g., treatment with erythropoiesis-stimulating agents).

Therapy for iron deficiency anemia (IDA) includes repletion of iron stores and, appropriate, correction of the underlying cause of iron loss.[1]

Oral iron is usually the appropriate initial treatment for anemia due to absolute iron deficiency, but a significant proportion of patients will not respond adequately. This may be due to poor compliance secondary to gastrointestinal side effects which include nausea, vomiting, and cramping. Also oral iron may be inappropriate in conditions of severe IDA in which oral iron may not be able to replenish iron stores rapidly enough to avoid blood transfusion.[1,2] Intravenous (I.V) iron, is the preferred therapy for such patients. However, earlier-generation parenteral therapies have been associated with bioactive iron reactions characterized by

hypotension, chest and abdominal pain, vomiting, and diarrhea (e.g., sodium ferric gluconate, iron sucrose) that limit the amount of iron that can be administered in a single dose to 100 to 200 mg. A typical therapeutic course of such agents requires 5 to 10 injections and multiple clinic visits. For these circumstances a variety of intravenous iron preparations have been developed.

There were two newer iron formulations permit much higher single doses of I.V iron to be administered over shorter periods of time.

- Ferumoxytol, an iron oxide with a carbohydrate coating, has demonstrated superiority over oral iron supplementation in patients with chronic kidney disease (CKD) and was approved by the Food and Drug Administration in 2009. The recommended dose is two 510 mg injections, 3 to 8 days apart.[3]
- Ferric carboxymaltose (FCM)) is a stable, non dextran I.V iron preparation whose properties permit administration of single doses of 750 to 1000 mg over short intervals.[3] It may be administered either as an undiluted slow I.V push at the rate of approximately 100 mg/min (i.e. over 7-8 min) or by infusion, in which case 750 mg of FCM is diluted in up to 250 ml of 0.9% sodium chloride solution and administered over at least 15 min.[1]

The aims of the present article are:

- To outline the frequency and outcomes of reactions to I.V iron,
- To indicate the risk factors for reactions to I.V iron; and
- To provide comprehensive guidance on risk minimization and management of iron infusions and acute reactions to them.

As authors are not aware of any existing guidance on how to avert and manage HSRs to this increasingly used treatment, and intend this paper to offer advice that has been developed from a comprehensive literature search and iterative expert review about best practice before, during and after administration of I.V iron to patients with IDA, primarily for healthcare professionals, whether they be doctors or nurses, who prescribe and administer I.V iron. In this report, authors refer to acute reactions to I.V iron as hypersensitivity reactions (HSRs), grading them into different types, depending on their clinical presentation.

CASE REPORT

Authors report a case of 23-year-old female came to general OPD of a tertiary care hospital, with chief complains of irregular menses, weakness. Her family history was not significant. A detailed past history revealed that she had similar complains in past. She had blood pressure (120/82) and severe anemia (hemoglobin-5.4g/dl) at the time of presentation. With the preview of anemia, patient was admitted in ward and started on ferric carboxymaltose after a test dose (0.5ml) which she tolerated. Ferric carboxymaltose (Orofer) was planned to give on two days with a dose of 500mg (one vial) in 100ml normal saline intravenous over 30 mins on each day. The patient developed rashes 45 min after the first dose was completed on anterior and lateral aspect of neck (as shown in fig.1), after which the drug was stopped. She was managed with inj. hydrocortisone 100 mg and inj. Avil (1amp) i. v. stat. A diagnosis to allergy to ferric carboxymaltose i.e type I HSR was made.

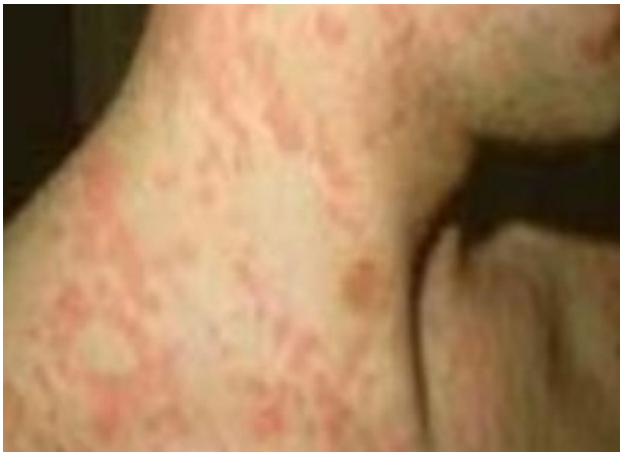

Figure 1: Rashes after 45 mins of administration of FCM.

Lab parameters

At the time of admission, the lab characteristics were as follows: random blood sugar-140mg/dl; fasting blood sugar- 90mg/dl; RBC- 3.95, Mycrocytic hypochromic RBCs, Hb- 5.4,

WBC- 6.8, Platelet-281, MCV- 44.4, sickling negative.

Treatment

Patient developed 20-25 rashes in anterior and lateral aspect of neck 45 minutes after completing the dose of ferric carboxymaltose. She was treated with a single dose of injection hydrocortisone 100mg i.v, injection Avil 1ampule I.V stat. Rashes subsided over 4 hours. Later on Tab Atrax 25mg BD and tab Allegra 120mg BD were given for 3 days. Patient recovered and was discharged. Other drugs given in this period were Cap Becasule 1 OD, Cap Autrin 1 OD and Tab Albendazole 400mg. Other drugs for her anaemia were continued.

DISCUSSION

Anaemia is a state where there is deficiency of oxygen carrying capacity of the erythrocytes in the blood. It can be classified based on nutritional deficiency, functional deficiency which causes blood loss and lack of production of erythrocytes. The nutritional elements for erythrocytes

are iron, vitamin B12 and folate. Deficiency of one of the component can cause anemia.[2]

More than 6 million women of reproductive age in the worldwide are iron deficient, and more than 3 million women have iron deficiency anemia(IDA). Hence the management of IDA is of great importance as it is most commonly seen in patients. IDA can be managed by oral and parenteral preparations. Parenteral iron therapy is given to patients, who are having chronic anaemia and cannot tolerate oral iron therapy. Ferrous sulphate, ferrous fumurate and ferrous gluconate are more commonly used. Phase II and III trials have demonstrated the efficacy and safety of FCM in patients of reproductive age group with heavy uterine bleeding or postpartum IDA.[1] Iron deficiency anemia in these women imposes a formidable disease burden that is rapidly treatable with large dose IV ferric carboxymaltose.[2]

FCM is a recently approved drug by FDA in July 2013. Ferric carboxymaltose is a colloidal iron hydroxide in complex with carboxymaltose, a carbohydrate polymer that releases iron.[4] Ferric carboxymaltose is a stable, newer non dextran IV iron preparation, with a near neutral pH, physiological osmolarity and increased bioavailability, whose properties permit administration of single doses of 750 to 1000 mg over short intervals.[5,6] The dose given above is well within the normal limits. These properties make FCM an attractive alternative to iron sucrose in terms of risk profile, efficacy, patient comfort and convenience, and also for staff and institutional resource utilization.

In multiple studies, FCM has been shown to be an effective option in the treatment of IDA, and it also improves the quality of life of patients.[7] The adverse effects like rashes (in form of allergy), vomiting, breathlessness and myalgia were also seen in the population who were involved in the clinical trial phases but these adverse reaction were rare (<1%), which is also known as type 1 Hypersensitivity reactions.[3,8] A fast iron infusion rate is a well-recognized risk factor, one possible explanation being the rapid increase in labile free iron. However, prevention of HSRs by reducing the speed of infusion is an effective practice not only with I.V iron but also with other reactogenic drugs.

As other probable causes like previous reaction to intravenous iron, fast iron infusion rate, history of other drug allergy or allergies, severe asthma or eczema, mastocytosis, severe respiratory or cardiac disease, old age, treatment with β-blockers, ACE inhibitors, pregnancy (first trimester) were not present in the female and this reaction started to appear within 45 mins. of administration of I.V FCM injection, there is a chronological relationship to intravenous FCM injection.[2] Hence, it was diagnosed as a case of adverse drug reaction to ferric carboxymaltose, which was 'mild' and 'preventable' according to Harting severity assessment and Schumock and Thornton scale respectively.[9,10]

According to World Health Organization causality assessment criteria, causality was determined as 'probable' due to FCM.[11] Using Naranjo's ADR probability scale, the causality assessment score of 2 was calculated, which again indicates that this reaction is 'probable' due to FCM.[12] However, for ethical constrains, authors did not perform FCM rechallenge. This adverse reaction was unpredictable and can be labelled as Type 'B' class of adverse reaction.[13] To the best of our literature search, authors came across very few previously reported cases of HSRs to FCM. So, authors are aimed to bring this into notice of physicians to prevent occurrence of such drug reactions

CONCLUSION

Authors thereby would like to conclude that all I.V iron preparations carry a small risk of adverse reactions which can be life-threatening if not treated promptly. However, the benefits of I.V iron overshadow its risks in the treatment of iron deficiency when the oral route is not sufficient or poorly tolerated. I.V iron products should only be administered, when well trained staff to assess and manage hypersensitivity reactions, with resuscitation facilities, are available. A test dose is not appropriate as it may give false assurance. Patients should be closely observed for signs of adverse events (HSRs) during and for at least 60 min after each administration. Special precautions are needed if I.V iron is to be given to patients with known allergies, severe atopy or systemic inflammatory diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis). Patients should also be instructed, to consult a healthcare professional immediately, if they develop any type of skin reaction while on treatment.

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