Case Report

Anaphylaxis with elevated serum tryptase after administration of intravenous ferumoxytol

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Abstract
Ferumoxytol is a newly approved preparation of intravenous iron with a modified dextran shell that is thought to confer upon it a low immunogenic potential. Serious adverse reactions have been very uncommon in clinical studies, but these studies excluded patients with prior adverse reactions to other preparations of intravenous iron. Furthermore, the reactions were classified clinically. We report on a patient with a history of hypersensitivity to iron dextran who experienced an anaphylactic reaction after receiving ferumoxytol. Laboratory testing revealed an elevated serum tryptase level, confirming mast cell activation. This is the first laboratory-proven case of anaphylaxis related to ferumoxytol.

Keywords: anaphylaxis; ferumoxytol; iron

Introduction
Parenteral iron has become a cornerstone in the management of anaemia in chronic kidney disease (CKD). Ferumoxytol (Feraheme, AMAG Pharmaceuticals Inc., MA, USA), which was FDA approved in June 2009 for the treatment of CKD-related anaemia, is composed of iron oxide with a carbohydrate shell composed of modified dextran (polyglucose sorbitol carboxymethyl ether). Available studies suggest that it is associated with a very low reported rate of serious adverse reactions. ‘Serious hypersensitivity reactions’ occurred in 0.2% of patients in a recently released FDA report [1]. These studies classified adverse reactions based on clinical presentation, and to date, there are no published reports of true anaphylaxis confirmed by laboratory testing. We report on a patient who experienced an adverse reaction to ferumoxytol clinically consistent with anaphylaxis, with the diagnosis supported by a markedly elevated serum tryptase level.

Case report

A 77-year-old black female patient with CKD stage 4 secondary to diabetes mellitus and hypertension received an intravenous infusion of ferumoxytol at an outpatient infusion centre for her CKD-related anaemia. Eight months prior to presentation, she had developed acute dyspnoea, hypotension and back pain during administration of intravenous iron dextran. Subsequently, she received six doses of intravenous iron sucrose without any complications. Other than iron dextran, she had no known drug hypersensitivities at the time of her ferumoxytol infusion. The patient's baseline laboratory data are shown in Table 1.

She was given ferumoxytol 510 mg over 1 min without any pre-medication. Twenty minutes after the infusion, the patient began experiencing pruritus on her abdomen and thighs, dyspnoea, wheezing, emesis, and tongue swelling. Her blood pressure fell from 130/49 mmHg pre-infusion to 111/49 mmHg, and her oxygen saturation by pulse oximetry fell from 99% on room air to ~80%. Treatment with oxygen via nasal cannula, diphenhydramine, intravenous famotidine and methylprednisolone followed by oral prednisone resulted in a complete resolution of symptoms over the next 2 days. Laboratory tests were significant for a tryptase level of 22.9 ng/mL (reference range <11.5 ng/mL).

Discussion
We report on a case of anaphylaxis related to the administration of intravenous ferumoxytol. To the best of our knowledge, there are no previously published reports of anaphylactic reactions to this drug with documented elevation of serum tryptase or other laboratory markers of anaphylaxis.

Concern over the toxicity of intravenous iron has long been a concern. Goetsch et al. [2] reported facial flushing, hypotension, tachycardia, nausea, vomiting and back pain in patients receiving intravenous ferric oxide or ferric hydroxide. Auerbach et al. [3] reported the frequent occurrence of fever, arthralgia and myalgia with iron dextran. These reactions may be mistaken for anaphylaxis, and the use of antihistamines to prevent/treat them can itself cause reactions which are then attributed to the iron [4]. Therefore, the documentation of a markedly elevated serum tryptase level, a specific marker of mast cell activation

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[5], is of special significance in this case in documenting anaphylaxis. The patient's prior reaction to iron dextran may have been anaphylactic but could also have been an instance of the arthralgia–myalgia syndrome described above. However, the constellation of signs and symptoms, including pruritus, dyspnoea, hypoxaemia and tongue swelling, along with the elevated serum tryptase, points very strongly to a diagnosis of anaphylaxis in the case of her reaction to ferumoxytol. Disorders other than anaphylaxis, such as systemic mastocytosis, acute myeloid leukaemia and some variants of hypereosinophilic syndrome, can be accompanied by elevated tryptase levels. In our patient, there was no clinical evidence of these disorders.

In the studies by Singh et al. and Provenzano et al., serious adverse reactions related to ferumoxytol were extremely uncommon [6,7]. Importantly, these studies excluded patients with a history of allergy to iron products or multiple drug allergies. To date, no clinical studies of ferumoxytol have included patients with documented allergy to other iron products. Ferumoxytol consists of iron nanoparticles coated with a modified dextran carbohydrate, which is thought to minimize its immunogenicity [8]. Our patient had had an adverse reaction to iron dextran in the past but had no other drug allergies. She had notably received several doses of iron sucrose without incident. It is unclear whether her reactions to ferumoxytol and iron dextran are coincidental or represent cross-reactivity to the carbohydrate moieties contained in the two drugs.

Traditionally, iron dextran has been considered to have a higher rate of serious adverse reactions than other available parenteral iron preparations. However, this may be largely attributable to the use of high-molecular-weight (HMW) dextran, and adverse reactions to low-molecular-weight (LMW) dextran appear to be much less common [9]. To date, no randomized controlled trials have directly compared two different parenteral iron formulations, so comparisons of the relative risk of adverse events have all been retrospective analyses. Coyne et al. [10] found that dextran-intolerant patients were more likely to react to both placebo and sodium ferric gluconate than dextran-tolerant patients. Their analysis concluded that these reactions were idiosyncratic and not true allergic responses. As mentioned above, studies of ferumoxytol have excluded patients with previous iron allergies, so similar comparative analyses are not yet possible.

In conclusion, our case demonstrates that true anaphylactic reactions to ferumoxytol can occur. The extremely low incidence of such reactions in previously published trials may be the result of patient selection. The safety of ferumoxytol in patients who have had adverse reactions to other iron formulations remains to be determined.

Conflict of interest statement. None declared.

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