Hypersensitivity from Intravenous Iron Products

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KEYWORDS

• Intravenous iron • Adverse drug reaction • Hypersensitivity • Toxicity

KEY POINTS

- Parenteral iron substitution is increasingly used.
- Immune complex anaphylaxis has rarely occurred to high-molecular-weight iron dextrans.
- Severe adverse drug reactions to newer carbohydrate iron formulations are very rare.
- So far, mechanisms have not been elucidated.

INTRODUCTION

Among many physicians, it is generally thought that intravenous (IV) iron has an inherent risk of serious adverse events (SAE). Earlier preparations of high-molecular-weight iron dextrans (HMW ID) were associated with rare SAE consistent with anaphylaxis. Newer formulations, which are discussed in this review, are safe, albeit rarely adverse drug reactions (ADR) may occur. Some ADR are fueled by the misinterpretation of clinical signs and mismanagement of minor infusion reactions.[1] When the literature is reviewed, it becomes obvious that clinically significant toxicity or hypersensitivity is extremely rare. Here the authors review the available IV iron formulations, the clinical manifestations of adverse reactions, their epidemiology and perceived pathophysiologic mechanisms, and management of adverse events.

TERMINOLOGY

ADR are not infrequent and may result in severe symptoms. A variety of terms have been used for different ADR patterns.[2] The most common ADR are correlated to known pharmacologic or toxic drug properties, are predictable, and may occur in any exposed individual (type A). Hypersensitivity reactions are less common,

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unpredictable, do not depend on pharmacologic properties, and usually occur in susceptible individuals (type B).[3] These latter ones are classified into immunologically mediated reactions, such as allergy and nonallergic hypersensitivity (intolerance or pseudoallergic reactions, also referred to as anaphylactoid), and idiosyncratic reactions. These latter terms are not generally accepted and are used inconsistently. In a consensus statement, the World Allergy Organization proposed that reactions without a proven specific immunologic mechanism be referred to as *nonallergic hypersensitivity reactions* and *pseudoallergy* and *anaphylactoid* should no longer be used.[4] The term *hypersensitivity* should be used to describe objectively reproducible symptoms or signs resembling allergy and initiated by exposure to a defined drug at a dose tolerated by normal subjects. Allergy is a hypersensitivity reaction initiated by specific immunologic mechanisms, either antibody mediated or cell mediated. In non–immunoglobulin E (IgE)–mediated allergy, inflammation involves IgG antibodies or allergen-specific lymphocytes. The adjectives *immediate* or *delayed* refer to the delay of onset of symptoms after the last drug administration[2] and may indicate the probable underlying immunologic mechanism (antibodies [IgE] in immediate or T cells in delayed reactions).

The term *anaphylaxis* is also used inconsistently. It has been proposed that *anaphylaxis* should be the general term for an acute reaction defined as a severe, life-threatening generalized or systemic hypersensitivity reaction. The term *allergic anaphylaxis* should be used when the reaction is mediated by an immunologic mechanism (IgE or immune complexes). Conversely, anaphylaxis caused by any nonimmunologic cause could be referred to as *nonallergic anaphylaxis*.[4] Anaphylaxis should affect at least 2 organ systems (eg, skin and respiratory tract or respiratory and gastrointestinal tract); however, if acute hypotension after a very probable elicitor occurs, *anaphylaxis* is an appropriate term.[5]

Here the authors use the term *immediate-type hypersensitivity* for clinical manifestations e. presenting with urticaria or, bronchospasm, likely involving mast cells and basophils, and *delayed-type hypersensitivity* for manifestations likely including T-cell mechanisms, such as exanthemas. The adjective *allergic* should be used only for immunologically mediated reactions. The authors prefer the term *nonimmunologic* to *nonallergic anaphylaxis* if no specific immune mechanism is proven as in most cases of immediate iron hypersensitivity reactions.

IRON COMPOUNDS AS POTENTIAL ALLERGENS

Iron, an essential trace element, is one of the most common elements on earth. It is estimated that a healthy adult contains 35 to 50 mg of iron per kilogram of body weight or a total of 2 to 6 g. At least 70% is used in hemoglobin, myoglobin, and enzymes involved in intracellular oxidation-reduction processes, oxygen transport, and cellular respiration. As 99% of red cell iron is recycled, the daily need is between 1 and 2 mg/d for an adult because of physiologic loss in sweat and stool.

Metals are haptens; in order to form a complete allergen, a carrier protein, which is typically an endogenous protein, is needed. For nickel and some other metals, particularly in the setting of contact allergy, direct binding to the HLA molecule has been demonstrated.[6] Additionally, it has been shown that nickel and cobalt may initiate an innate immune response in the sense of a danger signal[7] that is needed to induce an immunologic response. For any other metal, including iron, such a mechanism has not been studied. In humans, iron has been rarely demonstrated to have antigenic or allergenic properties.[8] Some metals, such as cobalt, which are also part of essential molecules, such as the vitamin B12 complex, are well-known contact allergens on topical cutaneous exposure.[9]