

Hypersensitivity from Intravenous Iron Products



Andreas J. Bircher, MD^{a,*}, Michael Auerbach, MD^{b,c}

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,

Disclosures: Dr A.J. Bircher has no relevant financial disclosures; Dr M. Auerbach has no relevant financial disclosures.

^a Allergy Unit, Dermatology Clinic, University Hospital Basel, Petersgraben 4, Basel 4031, Switzerland; ^b Georgetown University School of Medicine, 3900 Reservoir road northwest, Washington, DC 20007, USA; ^c Hematology and Oncology, Private Practice, King Avenue #308, Baltimore, MD 21237, USA

* Corresponding author.

E-mail address: andreas.bircher@unibas.ch

Immunol Allergy Clin N Am 34 (2014) 707–723

<http://dx.doi.org/10.1016/j.iac.2014.04.013>

immunology.theclinics.com

0889-8561/14/\$ – see front matter © 2014 Elsevier Inc. All rights reserved.

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 administration² 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 signal⁷ 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

To ensure better tolerance, iron products are administered in complexes as various salts or with carbohydrate carriers. A variety of different formulations are commercially available ([Table 1](#)). For HMW dextrans, also used as volume expanders¹⁰ and still used in some iron preparations, IgG-mediated anaphylaxis has been documented.¹¹ Immune complexes formed by specific IgG binding to HMW dextrans, as with iron dextran hypersensitivity, have been shown to elicit a so-called immune complex anaphylaxis (Coombs and Gell type III).¹² Preexisting high levels of IgG and IgM antibodies, so-called dextran-reactive antibodies, have been identified. Some other carbohydrates, such as carboxymethylcellulose (E466), are held responsible for rare cases of anaphylaxis on the intramuscular (IM) administration of corticosteroid preparations containing this emulsifying agent.^{13,14} Type I hypersensitivity is demonstrated here based on the presence of specific IgE. For other carbohydrates, such a mechanism has rarely been demonstrated. Recently, the disaccharide galactose- α -1,3-galactose has been shown to be an antigen in mammalian meat. The same antigen has been identified on the chimeric mouse/human antibody cetuximab, which has caused severe anaphylaxis on the first exposure in apparently previously sensitized patients.¹⁵

IRON PREPARATIONS

The liberation of catalytically active free iron is proportional to the instability of the carbohydrate complex and may lead to oxidative stress and hypotension.¹⁶ IV iron formulations are colloids that consist of spheroidal iron-carbohydrate nanoparticles.¹⁷ An iron-oxyhydroxide gel lies at the core of each particle. A shell of carbohydrate that stabilizes the iron-oxyhydroxide, slows down the release of bioactive iron, and maintains the resulting particles in colloidal suspension surrounds the core. IV iron agents share the same core chemistry but differ from each other by the size of the core and the type and density of the surrounding carbohydrate (see [Table 1](#)). Initially, only HMW ID were available and were associated with a high rate of anaphylactic reactions. The newer compounds have a considerably lower rate of ADR.

PATHOPHYSIOLOGY

Drug hypersensitivity reactions include all 4 Coombs and Gell types (types I–IV) as well as nonimmunologically mediated hypersensitivity reactions in which no specific initiating element, such as a drug-specific IgE-, IgG antibody, or T cell, can be demonstrated.¹⁸

In immediate IV iron hypersensitivity, several pathogenic models have been implicated. An IgE-mediated mechanism has not been convincingly shown.^{19,20} However, with HMW ID, immune complex anaphylaxis (Coombs and Gell type III)²¹ caused by preexisting dextran-reactive antibodies has been repeatedly demonstrated.²²

Hypersensitivity reactions to IV irons have similarities to the so-called red man syndrome related to IV vancomycin administration (by direct stimulation of mast cells). It is a nonimmunologic reaction and is thought to involve direct stimulation of mast cells or basophils. An increase in serum histamine levels,³ related to the rate of vancomycin infusion, has been shown. Therefore, it is recommended that vancomycin be administered over at least 1 hour.²³ The concomitant use of medications that cause nonspecific histamine release from mast cells may precipitate red man syndrome. Also, some infusion reactions from biologic drugs²⁴ show similarities (eg, toxicity caused by high doses or acute cytokine release [cytokine storm] caused by cell activation or cell death) that are also usually not immunologically mediated.²⁵ Other drugs include opioids, IV contrast agents, and muscle relaxants.²⁶

Table 1
Iron products and their properties

Trade name	Currently Available Intravenous Iron Preparations					Investigational Agents (Not FDA Approved)	
	DexFerrum	InFeD, Cosmofer	Ferlecit	Venofer	Ferumoxytol, Feraheme	Monofer Approved Europe	Injectafer Ferinject (Europe)
Carbohydrate	HMW ID (branched polysaccharide)	LMW ID (branched polysaccharide)	Gluconate (monosaccharide)	Sucrose (disaccharide)	Polyglucose sorbitol carboxy- methylether	Isomaltoside (linear oligosaccharide)	Carboxymaltose (branched polysaccharide)
Complex type	Type I; robust and strong	Type I; robust and strong	Type III; labile and weak	Type II; semirobust and moderately strong	Type I; robust and strong	Type I; robust and strong	Type I; robust and strong
Molecular weight measured by manufacturer (Da)	265,000	165,000	289,000–440,000	34,000–60,000	750,000	165,000	150,000
Labile iron release	–	–	+++	+/-	–	–	–
Total dose or >500-mg infusion	Yes	Yes	No	No	Yes	Yes	Yes

Premedication	TDI only	TDI only	No	No	No	No	No
Test dose required	Yes	Yes	No	No, yes ^a	No	No	No
Iron concentration (mg/mL)	50	50	12.5	20	30	100	30 50 (Europe)
Vial volume (mL)	1–2	2	5	5	17	1, 2, 5, 10	2, 10 1, 2, 10 (Europe)
Black box warning	Yes	Yes	No	No	No	No	No
Preservative	None	None	Benzyl alcohol	None	None	None	None

DexFerrum. Available at: <http://www.americanregent.com/documents/Product16PrescribingInformation.pdf>. Accessed September 4, 2013.

InFeD. Available at: http://pi.actavis.com/data_stream.asp?product_group=1251&p=pi&language=E. Accessed September 4, 2013.

Ferrlecit. Available at: <http://www.products.sanofi-aventis.us/ferrlecit/ferrlecit.pdf>. Accessed September 4, 2013.

Venofer. Available at: http://www.venofer.com/PDF/Venofer_IN2340_Rev_9_2012.pdf. Accessed September 4, 2013.

Feraheme. Available at: <http://www.feraheme.com/downloads/feraheme-pi.pdf>. Accessed September 4, 2013.

MonoFer. Available at: http://www.nataonline.com/sites/default/files/imagesC/Monofer_core_SPC.pdf. Accessed September 4, 2013.

Injectafer. Available at: http://www.injectafer.com/files/Prescribing_Information.pdf. Accessed September 4, 2013.

Abbreviations: FDA, Food and Drug Administration; LMW, low molecular weight; TDI, total dose infusion.

^a A test dose is only required in Europe.

Data from Macdougall I, Geisser P. Use of intravenous iron supplementation in chronic kidney disease: an update. *Iran J Kidney Dis* 2013;7(1):9–22; and Muñoz M, García-Erce JA, Remacha ÁF. Disorders of iron metabolism. Part II: iron deficiency and iron overload. *J Clin Pathol* 2011;64(4):287–96.

CLINICAL MANIFESTATIONS

Generally, hypersensitivity reactions from drugs may include a large variety of different clinical manifestations on different organs. The clinical manifestation is an expression of the involved mechanism. After the introduction of iron dextran products, anaphylactic reactions, including urticaria, angioedema, bronchospasm, and anaphylactic shock, have been reported.¹¹ Typical hypersensitivity symptoms are listed in **Box 1**.

HISTORY

To better understand the origin of negative perception with IV irons' use, a brief review of the history is necessary. In the early twentieth century, parenteral iron usage, often via the IM route, was limited because of prohibitive toxic reactions.²⁷ In 1947, Nissim²⁸ demonstrated that IV iron as saccharide could be administered with relative safety, although infusion reactions were common. Given the safety and efficacy of oral iron, it is not surprising that a paper by Marchasin and Wallerstein²⁹ received little attention, reporting 37 patients treated with a total dose infusion of iron dextran and none with SAEs.

In 1954, the first iron dextran, IMFeron, an HMW ID, (no longer available) was introduced by Baird and Padmore³⁰ for the treatment of iron deficiency by the IM route. It was used in divided doses with infrequent adverse events, such as pain and pigmentation at the injection site. Rare episodes of anaphylaxis were reported. In 1980, the first large prospective study of IV iron in the United States³¹ in 478 patients with iron deficiency who received full-dose replacement with HMW ID was published. Nearly all patients responded completely, but 3 had SAE; delayed reactions occurred in 8 patients, none of which were fatal. The researchers concluded that IV iron should only be used when iron deficiency cannot be treated adequately with oral iron. A black box warning was placed on the package insert that persists on all iron dextran products in the United States but not in Europe.

Box 1
Typical hypersensitivity symptoms to IV iron likely caused by an immune reaction

Immediate Symptoms

Skin: pruritus, extended flush, urticaria, angioedema

Respiratory: dyspnea, tachypnea, cough, bronchospasm, stridor

Gastrointestinal: nausea, emesis, colic, diarrhea

Cardiovascular: hypotension, hypertension, tachycardia, bradycardia, palpitations, chest pain, shock

Central nervous system: dizziness, syncope, unconsciousness

Delayed Symptoms

Fever

Arthralgia, arthritis

Lymphadenopathy

Exanthems

Data from Farnam K, Chang C, Teuber S, et al. Nonallergic drug hypersensitivity reactions. Int Arch Allergy Immunol 2012;159(4):327–45; and Hoigné R, Breymann C, Künzi UP, et al. Parenteral iron therapy: problems and possible solutions. Schweiz Med Wochenschr 1998;128(14):528–35 [in German].

In 1989, erythropoiesis-stimulating agents (ESA) became available for use in dialysis. This class of drugs promised to eliminate the symptoms of anemia. However, enthusiasm for the use of erythropoietin (EPO), the first ESA to be approved in the United States, was limited. At the same time, seminal work by Eschbach and colleagues³² and later Fishbane and colleagues³³ showed that when IV iron (but not oral) was given to hyporesponsive patients with iron-restricted erythropoiesis, marked synergy occurred. Iron dextran rapidly became standard in dialysis.

In 1991, IMFeron was removed from the market; but at the same time, a low-molecular-weight iron dextran (LMW ID), InFeD, became available. Between 1992 and 1996, virtually all patients undergoing dialysis received LMW ID. In 1996, another HMW ID (DexFerrum) was approved as an alternative. In 1999 and 2000, 2 iron salts, ferric gluconate (Ferrelecit) and iron sucrose (Venofer), were approved. Three retrospective studies on large dialysis populations,^{34–36} using spontaneous adverse event reporting systems, reported a much lower incidence of SAE; these 2 iron products rapidly replaced iron dextrans. In 2004, Chertow and colleagues³⁷ reported that most SAE were caused by the HMW ID formulation, which has been corroborated by the preponderance of published evidence.³⁸

Most of these concerns could have been precluded had the published evidence of Fishbane and colleagues³⁹ been more widely disseminated. They described an acute arthralgia and myalgia syndrome associated with the test dose. In 0.3% of patients, the acute onset of isolated chest oppression and back pain with or without facial flushing occurred (Box 2) but without further symptoms of anaphylaxis. After a short delay, symptoms resolved without treatment and rechallenges were tolerated. Unfortunately, these signs were considered as a prodrome to anaphylaxis; inappropriate intervention with drugs, such as diphenhydramine and epinephrine, converted a self-limited minor infusion reaction to a serious cardiovascular adverse event attributed to the IV iron. Similar misconceptions may arise when diphenhydramine is used as premedication for which there is no evidence to suggest a benefit. In a study of 135 patients receiving LMW ID preceded by premedication with cimetidine, dexamethasone, and diphenhydramine, most of the adverse events were considered secondary to premedication.⁴⁰

Recently, 3 new IV iron formulations that promise to allow complete replacement dosing in 15 minutes have been approved. These formulations are ferumoxytol (Feraheme), ferric carboxymaltose (Injectafer, Ferinject in Europe), and iron isomaltoside 1000 (Monofer, Europe only). Using head-to-head comparisons of LMW ID versus iron sucrose, ferumoxytol versus iron sucrose, and ferric carboxymaltose versus iron sucrose, no differences in efficacy or safety could be identified.^{41–45}

Box 2

Symptoms to IV iron likely caused by toxicity from free iron

Transient facial flushing
Chest oppression
Headache
Nausea, diarrhea
Back pain
Low-grade fever
Myalgia, arthralgia
If metallic taste, lower lumbar pain

ADR FROM IRON PRODUCTS

Reactions after the administration of IV iron can be divided into acute (immediately after the start of the infusion), delayed (hours to a day after the infusion), or long-term (mainly oxidative stress or infection). Although the literature is abundant with published evidence to theoretically support long-term reactions,⁴⁶ clinically relevant evidence is lacking. Following administration, iron is principally taken into the reticuloendothelial system where the carbohydrate shell is slowly degraded. Thus, elemental iron can be slowly released for erythropoiesis without causing toxicity. The metabolism of iron products is not similar to the physiologic iron process because IV administration bypasses the hepcidin-ferroportin pathway in the intestine, which protects against iron overload and regulates transferrin iron saturation.^{47–50}

Iron Products and Immediate Toxicity

Toxicity related to IV iron administration is attributed to the effects of bioactive labile iron (see [Box 2](#), [Fig. 1](#)). Yet, when appropriate dosing and proper administration protocols are followed, the symptoms are clinically insignificant, self-limited, and usually resolve without treatment. Furthermore, without any evidence, diphenhydramine is often used as premedication. This antihistamine is known to cause somnolence, diaphoresis, hypotension, and tachycardia; Barton and colleagues⁴⁰ reported that most adverse events were caused by the premedication with diphenhydramine.

To reduce the large amounts of labile iron causing toxicity, formulations were developed that shielded iron (see [Table 1](#)). Nonetheless, small amounts of labile iron are measurable following the administration of each formulation.⁵¹ The currently approved IV iron formulations all share the iron-carbohydrate structure but differ from each other by the size of the core and the density of the surrounding carbohydrate determining the amount of labile iron that is released (see [Table 1](#)).

Following the release of LMW ID for use as an adjunct to ESA in dialysis-associated anemia, marked improvements in hemoglobin responses, energy, activity, cardiovascular function, cognition, sexual function, and survival were observed; SAEs were extremely rare. However, after the release of HMW ID in 1996, a small but clinically significant increase in SAEs was observed. Faich and Strobos³⁴ compared the spontaneous reports to the US and European drug agencies of SAEs to iron dextrans and noniron dextrans and noted a significantly higher rate of reactions and 31 deaths attributed to the iron dextrans. No deaths caused by the nondextran irons were reported. In 2 retrospective analyses,^{35,36} a very low SAE rate with ferric gluconate as well as a negligible acute ADR rate even after previous iron dextran hypersensitivity were observed. It was subsequently concluded that ferric gluconate and iron sucrose were much safer than iron dextran, and more than 400,000 patients undergoing dialysis were switched from iron dextran to either ferric gluconate or iron sucrose.

Then in 2004, Chertow and colleagues³⁷ observed that most of the SAEs reported with iron dextran were caused by the HMW formulation and concluded that when HMW ID was avoided, SAEs were extremely rare, with an estimated incidence of less than 1:200,000 doses. Although using spontaneously reported ADR as an indicator of relative safety has been proscribed,⁵² every prospective study and intrainstitutional retrospective study comparing the safety of the iron salts with LMW ID has shown no difference.⁴⁶ Ferumoxytol and ferric carboxymaltose have been prospectively compared with iron sucrose for efficacy and safety. As with LMW ID, no significant differences have been noted.⁵³

An acute onset of arthralgia or myalgia and/or flushing may occur with any iron formulations. In extremely rare circumstances, these symptoms may be followed by

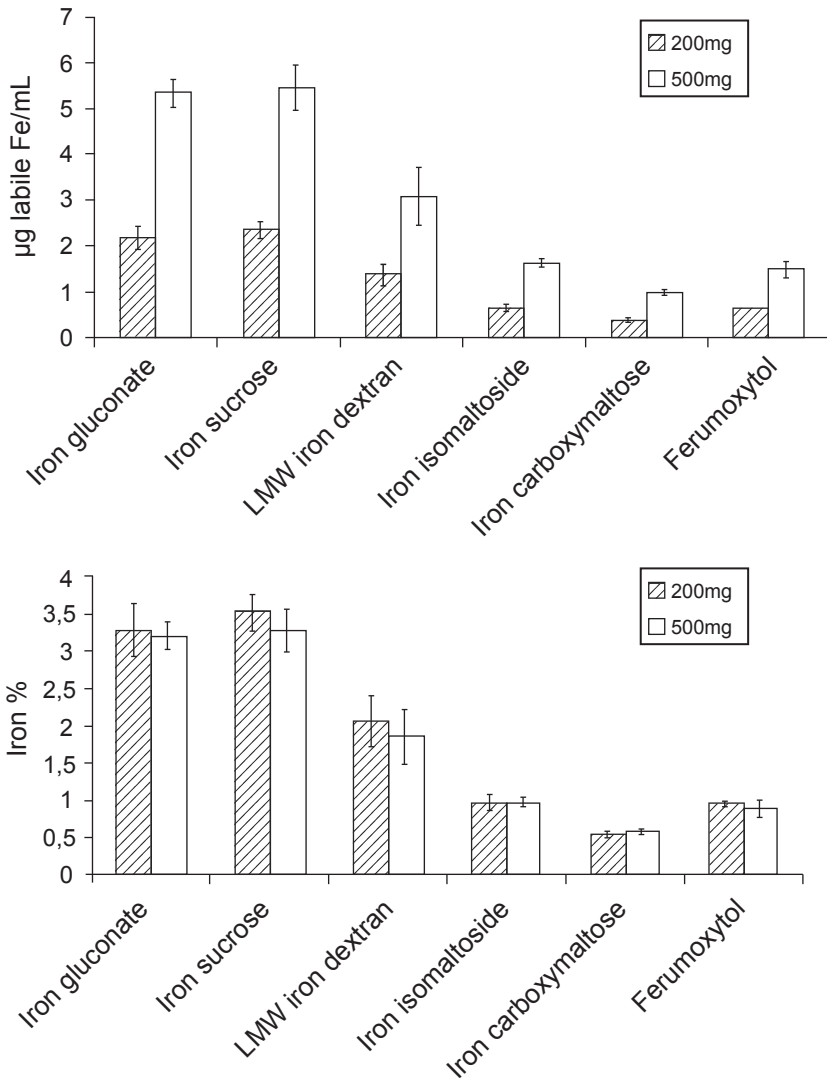


Fig. 1. Comparative labile iron pools of parenteral iron products. (*Upper diagram*) Concentration of the Ferrozine-detectable labile iron pool in µg/mL. The bars represent the average of at least 4 measurements. (*Lower diagram*) Ferrozine-detectable labile iron in percentage of the total used dose. For each measurement, the iron complex was incubated in human serum for 10 and 45 minutes, respectively. Thereafter, the Ferrozine reaction was performed; in each case, an intercept of a second-degree polynomial regression function of the absorption versus time curve with the ordinate was calculated. These intercepts were extrapolated to an incubation time of $t = 0$ (where t is time) by linear regression, yielding the labile iron pool in serum for each intravenous iron product. Fe, iron. (From Jahna MR, Andreasen HB, Fütterer S, et al. A comparative study of the physicochemical properties of iron isomaltoside 1000 (Monofer), a new intravenous iron preparation and its clinical implications. *Eur J Pharm Biopharm* 2011;78:486; with permission.)

anaphylaxis. It is of note, however, that no increase of serum tryptase levels, a serologic marker for anaphylaxis, was documented during these reactions.⁵⁴ Based on a validated tool, the Ferrozine-detectable iron, the amount of labile iron after administration of either 200 mg (ferric gluconate and iron sucrose) or 500 mg (LMW ID, ferumoxytol, ferric carboxymaltose, iron isomaltoside), is highest with the 2 salts, much lower with LMW ID, and lowest with ferumoxytol, ferric carboxymaltose, and iron isomaltoside (see Fig. 1).⁵¹ Therefore, the overwhelming likelihood is that they are minor systemic reactions to labile iron. These reactions resolve spontaneously and rarely recur with rechallenge. Pretreatment with methylprednisolone may decrease recurrence; in less than 1:1000 administrations, ranitidine and acetaminophen may be necessary.

Iron Products and Delayed Toxicity

Delayed arthralgias and myalgias infrequently occur after a total dose infusion or cumulative lower doses.⁵⁵ Premedication with corticosteroids abates or eliminates these reactions; but because they are mild and self-limited, the symptoms are also easily relieved with nonsteroidal antiinflammatory drugs. Other delayed reactions, with similar schedules, are low-grade fevers and headache.

Long-term toxicity remains a concern, but there are no prospective data on long-term outcomes with the use of IV iron. The most comprehensive work on this subject was done by Kalantar-Zadeh and colleagues⁵⁶ who examined time-dependent associations between IV iron administered and both all-cause and cardiovascular morbidity and mortality in patients undergoing maintenance hemodialysis. After extensive time-dependent and multivariate adjustment for case mix, administered IV iron and EPO doses, and surrogates of nutritional status and inflammation, the lowest all-cause and cardiovascular risk was associated with ferritin levels between 200 and 1200 ng/mL and transferrin saturations between 30% and 50%. Compared with those who did not receive IV iron, maintenance dosages of up to 400 mg per month were associated with improved survival. Supporting these conclusions, Feldman and colleagues⁵⁷ reported a slightly increased mortality in patients receiving more than 1 g of IV iron over a 6-month period; but after controlling for confounding variables, no morbidity with IV iron was present, thus, providing cautious support for the administration of greater than 1 g over a 6-month period if needed to maintain target hemoglobin.

Iron Products and Immediate Hypersensitivity

Despite the very rare occurrence of SAE,¹⁹ there are some case reports of severe anaphylaxis. In a 38-year-old woman, IV ferric gluconate 125 mg was given over 10 minutes. The first dose was initially well tolerated; however, nausea, dizziness, and minor tongue swelling occurred several minutes later.⁵⁸ On her second course of therapy, premedication with dexamethasone, diphenhydramine, and prochlorperazine was given. Subsequently, epigastric pain, nausea, swelling of her lips and tongue, and hypotension occurred. The symptoms resolved after the administration of diphenhydramine, dexamethasone, morphine, cimetidine, IV fluids, and oxygen. The Naranjo probability scale indicated a probable relationship between the hypersensitivity reaction and ferric gluconate, but no investigation was done.⁵⁸ A 24-year-old primigravida received ferric gluconate and developed tongue swelling. Diphenhydramine was given and the infusion was continued. Suddenly hypotension (70/30 mm Hg, pulse 110 beats per minute) and severe angioedema of the face and tongue developed. Resuscitation was successful, and she delivered a healthy child 1 week later.⁵⁹ No allergy investigation was performed. A 42-year-old woman received 100 mg of IV iron sucrose (Venofer); after 15 minutes, generalized pruritus, burning of the tongue, and peribuccal

hyperesthesia occurred.⁶⁰ Identical reactions occurred after premedication and iron sucrose and ferric carboxymaltose. Subsequent infusions were well tolerated. A patch test was negative, which is not surprising because it was likely the side effect of IV iron and not a T cell-mediated process. A particular case with a true allergic reaction to the casein component of oral iron proteinsuccinylate (Ferplex 40) was observed in a 4.5-year-old atopic child with a milk and fish allergy.⁶¹ A skin test and IgE were positive to milk proteins. An immunoblot revealed binding to the proteinsuccinylate, indicating its allergenic property.

Iron and Delayed-Type Hypersensitivity

Drug-induced exanthemas have been described with IV iron products, suggesting a T cell-mediated reaction; however, it is unlikely that iron is the elicitor. Unlike with nickel and palladium, contact allergy to iron seems to be extremely rare. Some researchers question the existence of true positive patch tests to iron because of the potential contamination of tested iron agents with other metal contact allergens, such as nickel or cobalt. There are very few cases with positive patch tests with iron.^{62,63} However, so far the optimal iron salt to be used in patch tests has not been established.

Iron and Long-term Toxicity and Infection

Human studies have shown transient increases in markers of oxidative stress with all forms of IV iron; however, no clinically negative outcomes associated with the increase in these markers has ever been reported.^{54,64}

IV iron has also been theoretically implicated as a possible cause of increased infection rates.^{65,66} However, no prospective study with defined infectious outcomes has ever shown an increase with millions of doses in dialysis-associated anemia, nondialysis chronic kidney disease, or chemotherapy-induced anemia, and several prospective and observational studies have shown the opposite.^{57,67,68} Eleven studies examining IV iron in chemotherapy-induced anemia have shown synergy with ESA when IV iron was added to the treatment paradigm. One additional study⁶⁹ observed a hemoglobin increment with IV iron alone. In 6 of the 12, whereby a defined infection rate was evaluated, no increment in infections was observed.^{69–74} This contention was corroborated in an extensive meta-analysis of IV iron in chemotherapy-induced anemia whereby no increment in infection was seen.⁷⁵ Finally, in a recent observational trial of 2547 perioperative patients who underwent elective lower limb arthroplasty or hip fracture repair, with or without ESA, observed not only reduced transfusion rates and length of hospital stay ($P = .0001$) but also no difference in infection rates.⁷⁶

In summary, the current state of the literature regarding the risk of IV and infection is inconclusive; but based on the preponderance of published evidence, the risk of IV iron, if any, in causing increased morbidity because of infections is vanishingly small.

DIAGNOSIS AND MANAGEMENT

An allergological work-up of a drug hypersensitivity reaction is based on the assumption of an antibody- or T cell-mediated process. Subsequent prick and intradermal tests are typically used for the identification of an IgE antibody-mediated reaction, whereas intradermal tests with late readings and patch tests are typically used for the diagnosis of T cell-mediated reactions with readings after 24 or 48 and 72 or 96 hours.⁷⁷ For metal antigens, neither specific IgE antibodies nor a cellular in vitro assay have so far been commercially established. Typically in occupational situations, such as inhalatory exposure to platinum salts⁷⁸ or in anaphylaxis to platinum salts used in oncology,⁷⁹ an IgE antibody-mediated mechanism has been implicated. For

other metals, this seems to be exceedingly rare. For immediate reactions basophil activation tests, that are used in drug hypersensitivity,^{80,81} and for T cell-mediated processes lymphocyte activation tests are feasible. The determination of specific IgG and IgM antibodies has been established for dextrans to detect immune complex reactions from dextrans used as plasma expanders or anticoagulants.⁸² However, for all in vitro tests, a standardized commercially available test is not on the market.

The only feasible test to identify a hypersensitivity reaction to a drug irrespective of the mechanism is a controlled reexposure or provocation test.⁸³ However, this carries the intrinsic danger of eliciting a life-threatening reaction. In some situations whereby a particular drug is indispensable, the procedure may help exclude a suspected hypersensitivity reaction.

If a patient has a probable hypersensitivity reaction after the administration of an iron product, the following information should be carefully obtained:

1. Brand and generic name of the product, including administered dose
2. Route of administration (perioral, IM, or IV [and velocity of infusion in the case of IV])
3. Morphology: exact description of clinical manifestations including all symptoms and signs (see "Clinical Manifestations"); nonspecific symptoms, such as metallic taste and lower lumbar pain, and so forth
4. Chronology: first onset of symptoms, their evolution, and disappearance
5. Response to treatment

From this description, a hypothesis on the potential mechanism can be made and the appropriate tests selected.

If suspected, a cutaneous or systemic mastocytosis should be excluded. The determination of baseline mast cell tryptase may be helpful in this situation. In the acute phase, mast cell tryptase can also be measured between 0.5 and 3.0 hours after the incident in order to demonstrate activation and mediator release from cutaneous mast cells.

For iron products, it is strongly discouraged to perform any prick or intradermal tests with undiluted or diluted solutions. First, an IgE-mediated mechanism, which could be identified by this technique, has not been demonstrated. Second, iron pigment may remain for prolonged periods. Skin tests for IgG-mediated reactions are not standardized and discouraged for the same aforementioned reasons. Finally, patch tests are only useful for T cell-mediated processes, such as eczema or exanthemas. These manifestations are exceedingly rare with iron, and the optimal patch test concentrations are not known. In vitro tests (such as the determination of specific IgG to potential antigens or allergens in iron formulations, basophil activation tests, and lymphocyte activation tests) are used in specialized laboratories for research purposes only.

Finally, provocation tests can be indicated in selected patients after a careful risk/benefit analysis.^{83,84} For some iron products, test doses are recommended without evidence to support the recommendation.¹ There are many reports of an initial mild reaction (eg, urticaria) not recurring with rechallenge with the same iron preparation. In some patients, the selection of another formulation may be advisable. In the authors' hands, this approach without premedication was successful in most patients with a putative hypersensitivity reaction to iron products.

The systematic premedication including antihistamines, corticosteroids, and leukotriene antagonists, as often done before IV radiocontrast media, is not recommended.⁸⁵ It has not been shown that premedication is of benefit⁵⁸; the premedication itself may lead to an ADR, including hypotension. In one patient, a so-called desensitization procedure with oral iron has been reported.⁸⁶

SUMMARY

Although adverse events occur with all the formulations of IV iron, the frequency of SAE in prospective studies is extremely low; but the current reporting systems provide scarce or no data at all about the relative frequency among the available formulations. IV iron is generally safe and probably much safer than most physicians realize. It is effective in treating iron deficiency across a broad spectrum of anemias. Unlike oral iron, which is rife with gastrointestinal perturbation, which is reported in up to 70% of those to whom it is prescribed, adherence is 100%. Published evidence supports a larger and earlier role for IV iron and raises the question of whether it should be the frontline therapy.

REFERENCES

1. Auerbach M, Ballard H, Glaspy J. Clinical update: intravenous iron for anaemia. *Lancet* 2007;369(9572):1502–4.
2. Palmiere C, Comment L, Mangin P. Allergic reactions following contrast material administration: nomenclature, classification, and mechanisms. *Int J Legal Med* 2014;128(1):95–103.
3. Farnam K, Chang C, Teuber S, et al. Nonallergic drug hypersensitivity reactions. *Int Arch Allergy Immunol* 2012;159(4):327–45.
4. Johansson SGO, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;113(5):832–6.
5. Sampson H, Muñoz Furlong A, Campbell R, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117(2):391–7.
6. Gamberdinger K, Moulon C, Karp DR, et al. A new type of metal recognition by human T cells: contact residues for peptide-independent bridging of T cell receptor and major histocompatibility complex by nickel. *J Exp Med* 2003;197(10):1345–53.
7. Schmidt M, Raghavan B, Müller V, et al. Crucial role for human Toll-like receptor 4 in the development of contact allergy to nickel. *Nat Immunol* 2010;11(9):814–9.
8. Lansdown AB. Physiological and toxicological changes in the skin resulting from the action and interaction of metal ions. *Crit Rev Toxicol* 1995;25(5):397–462.
9. Raghavan B, Martin S, Esser P, et al. Metal allergens nickel and cobalt facilitate TLR4 homodimerization independently of MD2. *EMBO Rep* 2012;13(12):1109–15.
10. Bircher AJ, Hédin H, Berglund A. Probable grade IV dextran-induced anaphylactic reaction despite hapten inhibition. *J Allergy Clin Immunol* 1995;95(2):633–4.
11. Bailie G, Clark J, Lane C, et al. Hypersensitivity reactions and deaths associated with intravenous iron preparations. *Nephrol Dial Transplant* 2005;20(7):1443–9.
12. Ring J, Behrendt H, de Weck A. History and classification of anaphylaxis. In: Ring J, editor. *Anaphylaxis chem immunol allergy*, vol. 95. Basel (Switzerland): Karger; 2010. p. 1–11.
13. Bircher AJ, Izakovic J, Bigliardi PL. Oral tolerance of carboxymethylcellulose in patients with anaphylaxis to parenteral carboxymethylcellulose. *Ann Allergy Asthma Immunol* 2004;92(5):580–1.

14. Bigliardi PL, Izakovic J, Weber JM, et al. Anaphylaxis to the carbohydrate carboxymethylcellulose in parenteral corticosteroid preparations. *Dermatology* 2003;207(1):100–3.
15. Wolver S, Sun D, Commins S, et al. A peculiar cause of anaphylaxis: no more steak? The journey to discovery of a newly recognized allergy to galactose-alpha-1,3-galactose found in mammalian meat. *J Gen Intern Med* 2013;28(2):322–5.
16. Potthoff SA, Münch HG. Safety aspects of parenteral iron supplementation therapies in patients with chronic kidney disease. *Dtsch Med Wochenschr* 2013;138(24):1312–7 [in German].
17. Danielson BG. Structure, chemistry, and pharmacokinetics of intravenous iron agents. *J Am Soc Nephrol* 2004;15(Suppl 2):S93–8.
18. Pichler WJ. Immune mechanism of drug hypersensitivity. *Immunol Allergy Clin North Am* 2004;24(3):373–97.
19. Novey HS, Pahl M, Haydik I, et al. Immunologic studies of anaphylaxis to iron dextran in patients on renal dialysis. *Ann Allergy* 1994;72(3):224–8.
20. Hoigné R, Breymann C, Künzi UP, et al. Parenteral iron therapy: problems and possible solutions. *Schweiz Med Wochenschr* 1998;128(14):528–35 [in German].
21. Zinderman C, Landow L, Wise R. Anaphylactoid reactions to dextran 40 and 70: reports to the United States Food and Drug Administration, 1969 to 2004. *J Vasc Surg* 2006;43(5):1004–9.
22. Kraft D, Hedin H, Richter W, et al. Immunoglobulin class and subclass distribution of dextran-reactive antibodies in human reactors and non reactors to clinical dextran. *Allergy* 1982;37(7):481–9.
23. Healy DP, Sahai JV, Fuller SH, et al. Vancomycin-induced histamine release and “red man syndrome”: comparison of 1- and 2-hour infusions. *Antimicrob Agents Chemother* 1990;34(4):550–4.
24. Scherer K, Spoerl D, Bircher AJ. Adverse drug reactions to biologics. *J Dtsch Dermatol Ges* 2010;8(6):411–26.
25. Vogel W. Infusion reactions: diagnosis, assessment, and management. *Clin J Oncol Nurs* 2010;14(2):E10–21.
26. Levy JH, Marty AT. Vancomycin and adverse drug reactions. *Crit Care Med* 1993;21(8):1107–8.
27. Auerbach M, Coyne D, Ballard H. Intravenous iron: from anathema to standard of care. *Am J Hematol* 2008;83(7):580–8.
28. Nissim JA. Intravenous administration of iron. *Lancet* 1947;2(6463):49–51.
29. Marchasin S, Wallerstein RO. The treatment of iron-deficiency anemia with intravenous iron dextran. *Blood* 1964;23(3):354–8.
30. Baird IM, Podmore DA. Intramuscular iron therapy in iron-deficiency anaemia. *Lancet* 1954;267(6845):942–6.
31. Hamstra RD, Block MH, Schocket AL. Intravenous iron dextran in clinical medicine. *JAMA* 1980;243(17):1726–31.
32. Eschbach JW, Kelly MR, Haley NR, et al. Treatment of the anemia of progressive renal failure with recombinant human erythropoietin. *N Engl J Med* 1989;321(3):158–63.
33. Fishbane S, Frei GL, Maesaka J. Reduction in recombinant human erythropoietin doses by the use of chronic intravenous iron supplementation. *Am J Kidney Dis* 1995;26(1):41–6.
34. Faich G, Strobos J. Sodium ferric gluconate complex in sucrose: safer intravenous iron therapy than iron dextrans. *Am J Kidney Dis* 1999;33(3):464–70.

35. Coyne D, Adkinson NF, Nissenson A, et al. Sodium ferric gluconate complex in hemodialysis patients. II. Adverse reactions in iron dextran-sensitive and dextran-tolerant patients. *Kidney Int* 2003;63(1):217–24.
36. Michael B, Coyne D, Fishbane S, et al. Sodium ferric gluconate complex in hemodialysis patients: adverse reactions compared to placebo and iron dextran. *Kidney Int* 2002;61(5):1830–9.
37. Chertow G, Mason P, Vaage Nilsen O, et al. On the relative safety of parenteral iron formulations. *Nephrol Dial Transplant* 2004;19(6):1571–5.
38. Rodgers G, Auerbach M, Cella D, et al. High-molecular weight iron dextran: a wolf in sheep's clothing? *J Am Soc Nephrol* 2008;19(5):833–4.
39. Fishbane S, Ungureanu VD, Maesaka JK, et al. The safety of intravenous iron dextran in hemodialysis patients. *Am J Kidney Dis* 1996;28(4):529–34.
40. Barton JC, Barton EH, Bertoli LF, et al. Intravenous iron dextran therapy in patients with iron deficiency and normal renal function who failed to respond to or did not tolerate oral iron supplementation. *Am J Med* 2000;109(1):27–32.
41. Okam M, Mandell E, Hevelone N, et al. Comparative rates of adverse events with different formulations of intravenous iron. *Am J Hematol* 2012;87(11):E123–4.
42. Sav T, Tokgoz B, Sipahioglu M, et al. Is there a difference between the allergic potencies of the iron sucrose and low molecular weight iron dextran? *Ren Fail* 2007;29(4):423–6.
43. Moniem KA, Bhandari S. Tolerability and efficacy of parenteral iron therapy in hemodialysis patients, a comparison of preparations. *Transfus Altern Transfus Med* 2007;9(1):37–42.
44. Critchley J, Dundar Y. Adverse events associated with intravenous iron infusion (low-molecular-weight iron dextran and iron sucrose): a systematic review. *Transfus Alternat Transfus Med* 2007;9(1):8–36.
45. Macdougall IC (1), Strauss WE, McLaughlin J, et al. A randomized comparison of ferumoxytol and iron sucrose for treating iron deficiency anemia in patients with CKD. *Clin J Am Soc Nephrol* 2014;9(4):705–12.
46. Auerbach M, Al Talib K. Low-molecular weight iron dextran and iron sucrose have similar comparative safety profiles in chronic kidney disease. *Kidney Int* 2008;73(5):528–30.
47. Coyne D. Hepcidin: clinical utility as a diagnostic tool and therapeutic target. *Kidney Int* 2011;80(3):240–4.
48. Rosner M, Auerbach M. Ferumoxytol for the treatment of iron deficiency. *Expert Rev Hematol* 2011;4(4):399–406.
49. Nemeth E, Tuttle M, Powelson J, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science* 2004;306(5704):2090–3.
50. Nemeth E, Ganz T. The role of hepcidin in iron metabolism. *Acta Haematol* 2009;122(2–3):78–86.
51. Jahn M, Andreasen H, Fütterer S, et al. A comparative study of the physico-chemical properties of iron isomaltoside 1000 (Monofer), a new intravenous iron preparation and its clinical implications. *Eur J Pharm Biopharm* 2011;78(3):480–91.
52. Wysowski D, Swartz L, Borders Hemphill BV, et al. Use of parenteral iron products and serious anaphylactic-type reactions. *Am J Hematol* 2010;85(9):650–4.
53. Onken JE, Bregman DB, Harrington RA, et al. Ferric carboxymaltose in patients with iron-deficiency anemia and impaired renal function: the REPAIR-IDA trial. *Nephrol Dial Transplant* 2014;29(4):833–42.

54. Auerbach M, Ballard H. Clinical use of intravenous iron: administration, efficacy, and safety. *Hematology Am Soc Hematol Educ Program* 2010;2010(1):338–47.
55. Auerbach M, Chaudhry M, Goldman H, et al. Value of methylprednisolone in prevention of the arthralgia-myalgia syndrome associated with the total dose infusion of iron dextran: a double blind randomized trial. *J Lab Clin Med* 1998;131(3):257–60.
56. Kalantar-Zadeh K, Regidor DL, McAllister CJ, et al. Time-dependent associations between iron and mortality in hemodialysis patients. *J Am Soc Nephrol* 2005;16(10):3070–80.
57. Feldman H, Joffe M, Robinson B, et al. Administration of parenteral iron and mortality among hemodialysis patients. *J Am Soc Nephrol* 2004;15(6):1623–32.
58. Saadeh C, Srkalovic G. Acute hypersensitivity reaction to ferric gluconate in a premedicated patient. *Ann Pharmacother* 2005;39(12):2124–7.
59. Cuciti C, Mayer DC, Arnette R, et al. Anaphylactoid reaction to intravenous sodium ferric gluconate complex during pregnancy. *Int J Obstet Anesth* 2005;14(4):362–4.
60. Sirvent-Pedreño A, Enríquez-Ascarza R, Redondo-Pachón MD, et al. Adverse reaction to intravenous iron: hypersensitivity or secondary side effect? *Nefrología* 2013;33(1):148–9.
61. Larramendi C, Marco F, García-Abujeta J, et al. Acute allergic reaction to an iron compound in a milk-allergic patient. *Pediatr Allergy Immunol* 2006;17(3):230–3.
62. Nater JP. Epidermale Überempfindlichkeit gegen Eisen. *Hautarzt* 1960;11:223–4.
63. Baer RL. Allergic contact sensitization to iron. *J Allergy Clin Immunol* 1973;51(7):35–8.
64. Scheiber Mojdehkar B, Lutzky B, Schaufler R, et al. Non-transferrin-bound iron in the serum of hemodialysis patients who receive ferric saccharate: no correlation to peroxide generation. *J Am Soc Nephrol* 2004;15(6):1648–55.
65. Brewster U, Perazella M. Intravenous iron and the risk of infection in end-stage renal disease patients. *Semin Dial* 2004;17(1):57–60.
66. Bullen J, Rogers H, Spalding P, et al. Iron and infection: the heart of the matter. *FEMS Immunol Med Microbiol* 2005;43(3):325–30.
67. Hoen B, Paul Dauphin A, Kessler M. Intravenous iron administration does not significantly increase the risk of bacteremia in chronic hemodialysis patients. *Clin Nephrol* 2002;57(6):457–61.
68. Brookhart MA, Freburger J, Ellis A, et al. Infection risk with bolus versus maintenance iron supplementation in hemodialysis patients. *J Am Soc Nephrol* 2013;24(7):1151–8.
69. Steinmetz T, Tschechne B, Harlin O, et al. Clinical experience with ferric carboxymaltose in the treatment of cancer- and chemotherapy-associated anaemia. *Ann Oncol* 2013;24(2):475–82.
70. Beguin Y, Maertens J, De Prijck B, et al. Darbepoetin-alfa and intravenous iron administration after autologous hematopoietic stem cell transplantation: a prospective multicenter randomized trial. *Am J Hematol* 2013;88(12):990–6.
71. Pedrazzoli P, Farris A, Del Prete S, et al. Randomized trial of intravenous iron supplementation in patients with chemotherapy-related anemia without iron deficiency treated with darbepoetin alpha. *J Clin Oncol* 2008;26(10):1619–25.
72. Henry D, Dahl N, Auerbach M, et al. Intravenous ferric gluconate significantly improves response to epoetin alfa versus oral iron or no iron in anemic patients with cancer receiving chemotherapy. *Oncologist* 2007;12(2):231–42.

73. Hedenus M, Birgegård G, Näsman P, et al. Addition of intravenous iron to epoetin beta increases hemoglobin response and decreases epoetin dose requirement in anemic patients with lymphoproliferative malignancies: a randomized multicenter study. *Leukemia* 2007;21(4):627–32.
74. Steensma D, Sloan J, Dakhil S, et al. Phase III, randomized study of the effects of parenteral iron, oral iron, or no iron supplementation on the erythropoietic response to darbepoetin alfa for patients with chemotherapy-associated anemia. *J Clin Oncol* 2011;29(1):97–105.
75. Gafter Gvili A, Rozen Zvi B, Vidal L, et al. Intravenous iron supplementation for the treatment of chemotherapy-induced anaemia - systematic review and meta-analysis of randomised controlled trials. *Acta Oncol* 2013;52(1):18–29.
76. Muñoz M, Gómez-Ramírez S, Cuenca J, et al. Very-short-term perioperative intravenous iron administration and postoperative outcome in major orthopedic surgery: a pooled analysis of observational data from 2547 patients. *Transfusion* 2014;54(2):289–99.
77. Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs – an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013;68(6):702–12.
78. Baur X, Bakehe P. Allergens causing occupational asthma: an evidence-based evaluation of the literature. *Int Arch Occup Environ Health* 2014;87(4):339–63.
79. Makrilia N, Syrigou E, Kaklamanos I, et al. Hypersensitivity reactions associated with platinum antineoplastic agents: a systematic review. *Met Based Drugs* 2010;2010. pii:207084.
80. Ebo DG, Leysen J, Mayorga C, et al. The in vitro diagnosis of drug allergy: status and perspectives. *Allergy* 2011;66(10):1275–86.
81. Leysen J, Sabato V, Verweij M, et al. The basophil activation test in the diagnosis of immediate drug hypersensitivity. *Expert Rev Clin Immunol* 2011;7(3):349–55.
82. Ljungström KG. Safety of dextran in relation to other colloids—ten years experience with hapten inhibition. *Infusionsther Transfusionsmed* 1993;20(5):206–10.
83. Aberer W, Bircher A, Romano A, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* 2003;58(9):854–63.
84. Cernadas JR, Brockow K, Romano A, et al. General considerations on rapid desensitization for drug hypersensitivity – a consensus statement. *Allergy* 2010;65(11):1357–66.
85. Brockow K, Romano A, Aberer W, et al. Skin testing in patients with hypersensitivity reactions to iodinated contrast media – a European multicenter study. *Allergy* 2009;64(2):234–41.
86. de Barrio M, Fuentes V, Tornero P, et al. Anaphylaxis to oral iron salts. Desensitization protocol for tolerance induction. *J Investig Allergol Clin Immunol* 2008;18(4):305–8.