REVIEW

OPEN

Safety of intravenous iron use in chronic kidney disease

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Purpose of review
Iron deficiency anaemia (IDA) is common and associated with fatigue, reduced quality of life and poorer clinical outcomes. Treatment with oral iron is often inadequate and international guidelines recommend intravenous (i.v.) iron as the preferred option for the treatment of IDA in certain clinical situations. In this review, we assess the safety of using i.v. iron with a particular focus on patients with chronic kidney disease.

Recent findings
Recent publications have raised safety concerns regarding the incidence of serious reactions accompanying i.v. infusion, as well as the subsequent risk of infections and cardiovascular events. Methodological flaws influence the interpretation of these data that lack evidence from the use of modern irons. The latter have been investigated in several randomized control trials.

Summary
There is a need for better understanding and definition of the nature of i.v. iron reactions, as many are nonserious infusion reactions rather than true anaphylaxis. Retrospective identification of anaphylaxis is difficult and we suggest the importance of reanalysing data using fatalities or standardized terms as outcome measures. With the exception of high molecular weight iron dextran, serious or life-threatening reactions are rare with the use of i.v. irons, and they can be used safely for the treatment of IDA.

Keywords
anaphylaxis risk, chronic kidney disease, intravenous iron, iron deficiency anaemia

INTRODUCTION

Iron deficiency anaemia (IDA) is a major health problem worldwide and it is commonly associated with chronic diseases such as chronic kidney disease (CKD) [1]. IDA is associated with fatigue, reduced quality of life, progression of disease, and poorer clinical outcomes [1–3]. Oral iron preparations may not be adequate for use in all patients because of intolerance, impaired absorption because of inflammation, and large iron deficits [4]. Therefore, intravenous (i.v.) iron is being increasingly used in patients not responding to oral iron. Moreover, some international guidelines recommend i.v. iron as the preferred option in the treatment of IDA in circumstances where there is decreased transport capacity and a high iron demand, as it is more effective and better tolerated than oral iron [5–7]. Currently, ferric carboxymaltose (Ferinject/Injectafer; Vifor Pharma, Zurich, Switzerland), ferric gluconate (Ferrlecit; Sanofi-Aventis U.S. LLC, Bridgewater, NJ, USA), ferumoxytol (Feraheme; AMAG Pharmaceuticals, Inc., Waltham, MA, USA), high molecular weight (HMW) iron dextran (Dexiron/Dexferrum; Luitpold Pharmaceuticals, Shirley, NY, USA), low molecular weight iron dextran (Cosmofer/Infed; Pharmacosmos A/S, Holbaek, Denmark), iron isomaltoside (Monofer; Pharmacosmos A/S), and iron sucrose (Venofer; Vifor Pharma) are available for use in clinical practice. All are considered efficacious in equivalent doses for

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KEY POINTS

- Oral iron is often insufficient for the correction of IDA in chronic disease because of intolerance, abnormal absorption, nonadherence, and large iron deficits; international guidelines recommend i.v. iron as the preferred option in the treatment of IDA in some patients.
- Retrospective identification of anaphylaxis is difficult and we recommend new approaches for reanalysing data using fatalities or standardized terms as outcome measures.
- Third generation i.v. irons have a low frequency of serious and severe hypersensitivity.
- Intravenous irons that are stable and have lower labile iron release, with reduced likelihood of cellular toxicity, are perhaps a preferable option.
- With the exception of HMW iron dextran, anaphylactic shock-type reactions are very rare with the use of i.v. irons. Other i.v. iron preparations can be used safely in the treatment of IDA, albeit with the appropriate use of caution that is required for any i.v. infusion.

treating anaemia, but they differ in their dose ranges, the duration and frequency of administration, and in their safety profiles.

Owing to the potential risk of anaphylactic reactions with the use of HMW iron dextran, some clinicians express concern about using i.v. iron for the treatment of IDA. Second-generation i.v. iron formulations, such as ferric gluconate and iron sucrose, have a lower frequency of anaphylactic reactions, and they became widespread in the treatment of IDA. However, large-dose administration is not possible with these agents and a typical iron deficit of 1000–2000 mg would require several visits. The introduction of the third-generation i.v. irons, ferric carboxymaltose and iron isomaltoside, resolved this limitation. In this review, we assess the safety of using i.v. iron, with particular focus on patients with CKD.

REVIEW METHODOLOGY

A literature search was conducted in May 2016 that covered the i.v. iron literature published since January 2015. Information was obtained from *PubMed* using the keywords 'intravenous' and 'iron' in the title/abstract. A total of 365 articles were identified, of which 37 were considered relevant to the topic. These articles were studied, and the most significant or novel are referred to in the current review. In addition, 36 important references are included, which were either published before January 2015 or not included in the *PubMed* database, for example, regulatory documents, guidelines, and the Standardised Medical Dictionary for Regulatory Activities (MedDRA) homepage.

CONCERNS WITH THE SAFETY OF INTRAVENOUS IRON

Hypersensitivity (including anaphylactic) reactions

It is well recognized that many medications can cause an allergic reaction and potential anaphylaxis [8]. HMW iron dextran has been associated with an increased risk of anaphylaxis, whereas these reactions are rarely observed with the more novel irons [9–14]. Wang *et al.* [15▪▪] compared the relative risk (RR) of anaphylaxis among i.v. iron dextran, ferric gluconate, iron sucrose, and ferumoxytol. The analysis included retrospective cohort studies of i.v. iron administered to iron-naïve patients ($n = 688\,183$) registered in the US fee-for-service Medicare program (January 2003 to December 2013). The first exposure risk for anaphylaxis was 68/100 000 persons [95% confidence interval (CI): 57.8–78.7] for iron dextran and 24/100 000 persons (95% CI: 20.0–29.5) for the other three nondextran i.v. iron products combined with an adjusted odds ratio of 2.6 (95% CI: 2.0–3.3; $P < 0.001$). Hence, the risk of one 'anaphylaxis' event appeared to occur in every 1500–4000 infusions. However, there are several methodological issues with this study, as discussed by DeLoughery and Auerbach [16▪▪]. The authors did not distinguish between HMW and low molecular weight iron dextrans and the diagnosis of anaphylaxis was derived from an algorithm based on International Classification of Diseases, Ninth Revision codes; one of the criteria was a combination of codes for allergies, symptoms, and treatments such as the administration of diphenhydramine and steroids. The algorithm allowed a patient to be classified as having 'anaphylaxis' simply by having received a premedication, rather than having definite evidence of a hypersensitivity reaction. No case note review to verify the nature of the 'anaphylactic' events was undertaken and the authors did not comment on mortality related to anaphylaxis. However, mortality data could be derived from the supplemental data provided. Fatal reactions on the day of iron administration for the period 2003–2013 were far lower, occurring between once every 12 500 and 25 000 infusions, with fatalities being greater with the other three irons compared with iron dextran (RR: 2.07, 95% CI: 0.99–4.78, $P = 0.04$).

Nature of intravenous iron reactions

A major problem is that many i.v. iron reactions are incorrectly classed as anaphylaxis. The classical definition of anaphylaxis is a serious, potentially life-threatening allergic reaction that typically develops quickly (minutes to a few hours) and may cause death because of circulatory collapse or bronchospasm, and usually requires immediate treatment. However, there are other more frequent reactions, such as labile iron reactions and the 'Fishbane' reaction, that might be mistakenly reported as anaphylaxis reactions [17]. The retrospective identification of anaphylaxis is therefore difficult and clinicians define the term differently and there is no consensus on what to report and when. Therefore, the use of hard clinical endpoints, such as fatalities, appears to be the most undisputable outcome measure.

Although adverse events occur with i.v. iron, the frequency of serious adverse drug reactions (ADRs, related adverse events) in prospective trials is very low and impossible to investigate comparatively in randomized controlled trials (RCTs). Furthermore, the majority of RCT have only a short follow-up period (and drug exposure) and are inadequate to assess the long-term safety and mortality risk [18]. Instead postmarketing reporting of such events could be used to estimate the frequencies [11,12]. Postmarketing safety data are, however, inherently unreliable as they are subject to numerous biases. As mentioned above, identification of anaphylaxis is difficult and clinicians define the term differently. An algorithm outlining grading and management of acute hypersensitivity reactions to i.v. iron infusions can be found in the review by Rampton *et al.* [19] and recent studies by Szebeni *et al.* [20] and Macdougall *et al.* [21], the latter summarized in a document published after a Kidney Disease: Improving Global Outcomes (KDIGO) expert conference on iron controversies.

Another method to standardize the definition of anaphylactic reactions is to use the MedDRA Queries (SMQs) applied in pivotal regulatory trials in the United States. SMQs are validated, standard sets of MedDRA terms, which have undergone extensive review, testing, analysis, and expert discussion by a working group of MedDRA and product safety experts [22]. The SMQs for anaphylactic reaction include hypersensitivity/allergic reactions and any serious or severe treatment-emergent adverse event occurring on the day of or the day after dosing. The SMQs for anaphylactic groups of specific terms can be found in Table 1. Use of such standardized terms in the setting of rigorously conducted prospective Good Clinical Practice trials for regulatory approval are likely to avoid many of the biases with retrospective studies such as the above study by Wang *et al.* [15▪▪]. In general, the modern i.v. irons have very low frequencies of severe and serious hypersensitivity reactions (Table 2).

Risk of infection

It has been postulated that i.v. iron might promote infection [24] but there are conflicting studies in the literature. The risk of infection is thought partly to be because of some i.v. irons having a potentially immunoactivating effect; for example, less stable i.v. irons, such as iron sucrose, induce phenotypical and functional monocytic alterations [25], and have a higher potential to modulate monocyte differentiation to macrophages and mature dendritic cells than more stable preparations [26]. A few small trials in CKD populations suggest an increased infection risk with i.v. iron [27,28▪▪]. Agarwal *et al.* [28▪▪] undertook a single-centre RCT that randomly assigned nondialysis-dependent CKD (NDD-CKD) patients with IDA to either oral iron (69 patients) or i.v. iron sucrose (67 patients); the primary endpoint examined whether i.v. iron influenced the rate of loss of renal function with time. As a secondary outcome measure, they found an increase in serious adverse events (SAEs) because of infections in patients receiving i.v. iron, with infections in the oral iron group occurring 27 times in 11 patients, whereas in the i.v. iron group, they occurred 37 times in 19 patients; the adjusted RR ratio was 2.12 (1.24–3.64), $P < 0.006$ [28▪▪]. Litton *et al.* [29] published a systematic review and meta-analysis of RCT to investigate the safety and efficacy of i.v. iron therapy. They obtained data from *Medline*, *Embase*, and the *Cochrane Central Register of Controlled Trials* from 1966 to June 2013. In total, 72 trials with 10 605 patients were included. Intravenous iron was found to be associated with a significant increase in RR of infection of 1.33 (95% CI: 1.10–1.64) compared with oral or no iron supplementation [29]. However, these findings were subject to bias as infection was not a predefined endpoint in many of the trials that were included in the meta-analysis. They could also not detect a dose–response association between iron and risk of infection, further undermining the causal relationship [30]; and these limitations were acknowledged by the authors.

Other studies have shown contrasting results regarding risk of infections associated with i.v. iron [31–33]. In another meta-analysis that included 103 RCT, Avni *et al.* [34▪] concluded that there was no increased risk of infections with the use of i.v. irons. Ishida *et al.* [35▪] published a retrospective observational cohort study using

Table 1. Regulatory standardized Medical Dictionary for Regulatory Activities Queries terms for the definition of hypersensitivity events

SMQ terms			
Group A	Group B	Group C	Group D
Narrow terms pertaining to hypersensitivity reactions	Broad terms pertaining to respiratory reactions potentially related to hypersensitivity	Broad terms pertaining to skin reactions potentially related to hypersensitivity	Broad terms pertaining to cardiovascular reaction potentially related to hypersensitivity
Anaphylactic reaction	Acute respiratory failure	Allergic oedema	Blood pressure decreased
Anaphylactic shock	Asthma	Angioedema	DBP decreased
Anaphylactic transfusion reaction	Bronchial oedema	Erythema	SBP decreased
Anaphylactoid reaction	Bronchospasm	Eye oedema	Cardiac arrest
Anaphylactoid shock	Cardiorespiratory distress	Eye pruritus	Cardiorespiratory arrest
Circulatory collapse	Chest discomfort	Eye swelling	Cardiovascular insufficiency
First-use syndrome	Choking	Eyelid oedema	Diastolic hypotension
Kounis syndrome	Choking sensation	Face oedema	Hypotension
Shock	Circumoral oedema	Flushing	
Type I hypersensitivity	Cough	Generalized erythema	
	Cyanosis	Injection site urticaria	
	Dyspnoea	Lip oedema	
	Hyperventilation	Lip swelling	
	Laryngeal dyspnoea	Ocular hyperaemia	
	Laryngeal oedema	Oedema	
	Laryngospasm	Periorbital oedema	
	Laryngotracheal oedema	Pruritus	
	Mouth swelling	Pruritus allergic	
	Nasal obstruction	Pruritus generalized	
	Oedema mouth	Rash	
	Oropharyngeal spasm	Rash erythematous	
	Oropharyngeal swelling	Rash generalized	
	Respiratory arrest	Rash pruritic	
	Respiratory distress	Skin swelling	
	Respiratory failure	Swelling	
	Reversible airways obstruction	Swelling face	
	Sensation of foreign body	Urticaria	
	Sneezing	Urticaria popular	
	Stridor		
	Swollen tongue		
	Tachypnoea		
	Throat tightness		
	Throat oedema		
	Tracheal obstruction		
	Tracheal oedema		
	Upper airway obstruction		
	Wheezing		

DBP, diastolic blood pressure; SBP, systolic blood pressure; SMQ, Medical Dictionary for Regulatory Activities Queries.

data from the US Renal Data System examining 22 820 adult Medicare beneficiaries receiving in-centre haemodialysis, who had been hospitalized for bacterial infection in 2010; 2463 (10.8%) had received i.v. iron in the 14 days preceding their hospitalization. Patients treated with i.v. iron did not have a higher 30-day mortality (odds ratio 0.86) or readmission rate for infection within

Table 2. Serious or severe hypersensitivity events on day or day after a dosing with intravenous iron, based upon Medical Dictionary for Regulatory Activities Queries terms for anaphylactic reactions

	Iron isomaltoside (*N* = 1729) *n* (%)	Ferric carboxymaltose (*N* = 1775) *n* (%)	Iron sucrose (*N* = 1503) *n* (%)	*P*[a]	*P*[b]	*P*[c]
At least one event	10 (0.6)	26 (1.5)	24 (1.6)	0.011	0.005	0.78
Group A	1 (0.06)	2 (0.1)	1 (0.1)	1.0	1.0	1.0
Group B	4 (0.2)	13 (0.7)	8 (0.5)	0.049	0.25	0.52
Group C	3 (0.2)	3 (0.2)	3 (0.2)	1.0	1.0	1.0
Group D	3 (0.2)	8 (0.5)	12 (0.8)	0.226	0.016	0.26
Group B + C	7 (0.4)	16 (0.9)	11 (0.7)	0.093	0.24	0.70
Group B + C + D	9 (0.5)	24 (1.4)	23 (1.5)	0.013	0.004	0.77
Group B + D	6 (0.4)	21 (1.2)	20 (1.3)	0.006	0.002	0.75

[a]Fisher's exact test for iron isomaltoside compared with ferric carboxymaltose.
[b]Fisher's exact test for iron isomaltoside compared with iron sucrose.
[c]Fisher's exact test for ferric carboxymaltose compared with iron sucrose.
Group A: narrow terms pertaining to hypersensitivity reactions, Group B: broad terms pertaining to respiratory reactions potentially related to hypersensitivity, Group C: broad terms pertaining to skin reactions potentially related to hypersensitivity, and Group D: broad terms pertaining to cardiovascular reactions potentially related to hypersensitivity. The specific terms included in each group can be found in Table 1.
The data for iron isomaltoside were based on clinical trial data provided by Pharmacosmos A/S and data for ferric carboxymaltose (pivotal trials) and iron sucrose was retrieved from the Center for Drug Evaluation and Research Medical Review Report evaluating ferric carboxymaltose as part of the US approval process [23].

30 days of discharge, compared with patients not receiving i.v. iron.

Risk of direct cellular damage and cardiovascular events

Another concern is that i.v. iron might cause endothelial damage and promote atherosclerosis by generating oxidative stress [34▪] with potential consequences of long-term cardiovascular toxicity. Intravenous iron has been shown to induce oxidative stress [36] as labile iron is able to generate highly reactive hydroxyl radicals by reacting with hydrogen peroxide in the Fenton reaction [37]. This is supported by a small study by Agarwal *et al.* [38] showing that iron sucrose induces oxidative stress associated with transient proteinuria and tubular damage in CKD patients. The direct toxic effect of iron on renal tubular cells appears greatest with iron sucrose and less with iron dextran and iron isomaltoside [39].

The single-centre RCT conducted by Agarwal *et al.* [28▪▪] has already been alluded to in the context of infection risk. However, that study of 136 NDD-CKD patients was halted early based on futility of the primary endpoint (failure to demonstrate differences in CKD progression) and because the RR of serious cardiovascular events was 2.51 for patients treated with i.v. iron. Cardiovascular events were nominally higher with i.v. iron but the number of patients developing these events was almost identical (there were 55 events in 17 patients treated with i.v. iron and 36 in 19 patients who received oral iron; $P = 0.033$).

These findings are inconsistent with the results of larger randomized trials [32,40▪] and we therefore feel that they should be interpreted with caution and warrant further study.

Other unwanted effects of intravenous iron

Intravenous irons differ in their capability to induce medically significant hypophosphatemia [41]. This has been reported most often with ferric carboxymaltose [42] arguing against a class effect; the mechanism is substance specific via an increase in fibroblast growth factor 23 [43,44]. This area requires further study to clarify the significance of these variable effects of i.v. iron preparations.

RECENT CLINICAL TRIALS SUPPORTING SAFETY

Kalra *et al.* [40▪] published a RCT conducted in 351 iron-deficient NDD-CKD patients receiving either iron isomaltoside or oral iron. ADRs were observed in 10.5 and 10.3% of the patients in the i.v. and oral iron groups, respectively. Three serious ADRs (two events of hypersensitivity in the i.v. iron group and one event of oesophagitis in the oral iron group) were reported. All patients fully recovered from the events. There were three fatal events in the i.v. iron group but none was drug related. All three patients had a significant prior history of cardiac disease; two elderly patients had decompensated heart failure for 6 weeks and 3 months, respectively, after i.v. iron, the other had pneumonia

complicated by myocardial infarction. More patients treated with oral iron were withdrawn from the trial because of adverse events (4.3%) than patients treated with i.v. iron (0.9%) [40▪]. In a larger RCT of iron-deficient NDD-CKD patients, Macdougall *et al.* [32] randomized 626 patients to either i.v. ferric carboxymaltose or oral iron. Approximately, 15 and 29% of the reported adverse events were considered treatment related in the ferric carboxymaltose and oral iron groups, respectively. Two patients in the ferric carboxymaltose group experienced a drug hypersensitivity reaction, one of which was graded mild and the other graded moderate in severity. Both patients fully recovered. One serious ADR was observed in the oral iron group. Adverse events leading to discontinuation occurred in approximately 4 and 13.5% of the patients in the ferric carboxymaltose and oral iron groups, respectively. In total, 25 patients died during the trial (10 in the ferric carboxymaltose group and 15 in the oral iron group) but none of the events was assessed as related to the trial drug [32].

Bhandari *et al.* [45▪] published a RCT conducted in 351 haemodialysis patients receiving either iron isomaltoside or iron sucrose. ADR were observed in 5.2 and 2.6% of the patients in the iron isomaltoside and iron sucrose groups, respectively. Three of these ADR were reported as serious; one was because of hypersensitivity in the iron isomaltoside group and there were ADR of staphylococcal bacteraemia and dyspnoea in the iron sucrose group. Three patients in the iron isomaltoside group died during the trial and an additional two patients died without being exposed to trial drug. In all cases, these events were deemed not related to the trial drug and the observed mortality was in line with the expected mortality in this population during the time frame of the RCT [45▪]. The meta-analysis by Avni *et al.* [34▪] has already been alluded to. In RCT (1965–2013) in which i.v. iron was trialled against a comparator agent, placebo, or no therapy, a total of 10 390 patients were treated with i.v. iron compared with 4044 patients treated with oral iron, 1329 with no iron, 3335 with placebo, and 155 with intramuscular iron. No increased risk of SAEs with i.v. iron was detectable in this analysis (RR, 1.04; 95% CI: 0.93–1.17) [34▪].

CONCLUSION

Owing to the relatively high risk of anaphylactic reactions observed with the historic i.v. irons, there has been some reluctance in the use of i.v. irons, and recent studies have suggested continued risk. However, investigating the frequencies of ADRs, especially anaphylactic reactions, is difficult as clinicians define the term differently and it is well recognized that milder reactions, which are usually self-limiting, may be misclassified as anaphylactic reactions. Using fatalities or SMQ terms as outcome measures might help in this matter as well as the algorithms provided by the KDIGO expert group (Macdougall *et al.* [21]), Rampton *et al.* [19], and Szebeni *et al.* [20]. Nonetheless, there is no doubt that the HMW iron dextrans are associated with increased risks, and therefore, these i.v. irons should be avoided [9–14].

The second and third-generation i.v. irons are considered equally efficacious in treating iron deficiency in equivalent doses but they differ in their stability [46], ability to induce oxidative stress [36–38], their effect on immune function [25,26], and dosing and administration options [47]. Iron isomaltoside seems to have a lower frequency of serious and severe hypersensitivity reactions, when using a novel approach of prospectively reported standardized medical terms pooled from different randomized trials. This is a promising approach for future research into the risk of serious hypersensitivity. In conclusion, with the exception of HMW iron dextran, serious or life-threatening reactions are very rare with the use of i.v. irons, and they can be used safely, albeit not overlooking the need for caution, in the treatment of IDA, including that frequently seen in CKD.

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Conflicts of interest

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- ▪ of special interest
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