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Original Article

On the relative safety of parenteral iron formulations

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Abstract

Background. Intravenous iron is usually required to optimize the correction of anaemia in persons with advanced chronic kidney disease and end-stage renal disease. Randomized clinical trials may have insufficient power to detect differences in the safety profiles of specific formulations.

Methods. We obtained data from the US Food and Drug Administration on reported adverse drug events (ADEs) related to the provision of three formulations of intravenous iron during 1998–2000. We estimated the relative risks [odds ratios (OR)] of ADEs associated with the use of higher molecular weight iron dextran and sodium ferric gluconate complex compared with lower molecular weight iron dextran using 2×2 tables.

Results. The total number of reported parenteral iron-related ADEs was 1981 among ~21 060 000 doses administered, yielding a rate of 9.4×10^{-5}, or ~94 per million. Total major ADEs were significantly increased among recipients of higher molecular weight iron dextran (OR 5.5, 95% CI 4.9–6.0) and sodium ferric gluconate complex (OR 6.2, 95% CI 5.4–7.2) compared with recipients of lower molecular weight iron dextran. We observed significantly higher rates of life-threatening ADEs, including death, anaphylactoid reaction, cardiac arrest and respiratory depression among users of higher molecular weight compared with lower molecular weight iron dextran. There was insufficient power to detect differences in life-threatening ADEs when comparing lower molecular weight iron dextran with sodium ferric gluconate complex.

Conclusions. Parenteral iron-related ADEs are rare. Using observational data, overall and most specific ADE rates were significantly higher among recipients of higher molecular weight iron dextran and sodium ferric gluconate complex than among recipients of lower molecular weight iron dextran. These data may help to guide clinical practice, as head-to-head clinical trials comparing different formulations of intravenous iron have not been conducted.

Keywords: adverse drug events; iron dextran; parenteral iron; sodium ferric gluconate complex

Introduction

Despite the use of recombinant erythropoietin, anaemia remains a significant problem for patients with advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD). Iron deficiency commonly complicates both conditions, and tends to be more severe among individuals on haemodialysis [1]. Blood loss into the haemodialyser system and routine discarding of small aliquots (5–10 ml) of blood (in patients using indwelling catheters) account for a large fraction of the blood loss seen in the haemodialysis population. Occult gastrointestinal haemorrhage, anticoagulation-related blood loss and accidental blood loss from arteriovenous fistulae and grafts also contribute to blood loss and iron deficiency. On average, maintenance haemodialysis is associated with a loss of at least 1–1.5 g of elemental iron each year [2].

Oral iron preparations have proved ineffective and relatively poorly tolerated in the ESRD population [3]. Comparative studies of oral versus parenteral iron administration have unequivocally established the superiority of intravenous preparations in replacing iron stores [4]. As a result, the use of parenteral iron in conjunction with erythropoietin has become standard practice in most maintenance haemodialysis programmes worldwide, and has been endorsed by professional societies in the USA, Europe and elsewhere [1,5].

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During the 1980s and 1990s, several fomulations of iron dextran were commercially available in the USA. While effective at repleting iron stores, enthusiasm for the use of these agents was tempered by the risk of adverse drug events (ADEs), especially anaphylaxis, associated with their use. Newer, non-dextran formulations of iron have been introduced, and have been marketed as equally effective and safer than iron dextran formulations.

Fletes *et al*. [6] recently reported on the frequency of iron dextran-related ADEs during a 6-month period using data derived from Fresenius Medical Care North America Clinical Variance Reports. In the current study, we aimed to extend our inquiry to the entire US haemodialysis population, using data reported to the US Food and Drug Administration (FDA) and obtained from the World Health Organization. Incorporating reports filed during the calendar years 1998–2000, we sought to estimate overall ADEs for two iron dextran preparations that differ in the molecular weight and structure of the dextran moiety (InFed® and Dexferrum®) and for sodium ferric gluconate complex (Ferrlecit®). We also sought to determine the relative frequency of specific ADEs. Since parenteral iron-related ADEs are rare, population-based cohort analyses are necessary to provide valid estimates of safety.

Materials and methods

All parenteral iron-related ADEs reported to the FDA during the calendar years 1998–2000 were obtained from the World Health Organization in Uppsala, Sweden. Deaths were reviewed in detail and duplicates were eliminated. Specific ADEs were categorized according to the FDA's system organ class criteria and summarized. Detailed clinical information, including dialysis status, on the affected individuals was not available.

The ADE rate was determined by dividing the number of overall or specific ADEs by the number of dose vials dispensed. The vial size of sodium ferric gluconate complex (62.5 mg) is lower than the vial size of the two iron dextran preparations (100 mg). Therefore, unadjusted ADE rates, and ADE rates adjusted per 100 mg of iron dispensed for the ferric gluconate in sucrose solution, were calculated.

We classified 17 types of ADEs as serious ADEs. These included: death, cardiac arrest, myocardial infarction, coma, anaphylactic shock, anaphylactoid reactions, seizures, arrhythmia, apnoea, respiratory depression, tachycardia, bradycardia, allergic reaction, hypertension, hypotension, cyanosis and urticaria. We further subclassified ADEs into life-threatening (death, anaphylactoid reactions, cardiac arrest and respiratory depression) and non-life-threatening ADEs (all others). Low molecular weight iron dextran (InFed® in the USA, Cosmofer® outside the USA) was used as the referent group. The relative risks [odds ratios (ORs)] of ADEs associated with high molecular weight iron dextran (Dexferrum®) and sodium ferric gluconate complex (Ferrlecit®) use were estimated from 2×2 tables. The level of statistical significance was determined by the Yates-corrected χ^2 test. Confidence intervals (CIs) were computed using the method of Fleiss [7]. Two-tailed *P*-values <0.05 were considered statistically significant.

Results

Frequency of ADEs

The total number of reported parenteral iron-related ADEs was 1981 among ~21 060 000 doses administered, yielding a rate of 9.4×10^{-5}, or ~94 per million. Twenty-one individuals died in association with an ADE (0.0001%). The number of patients affected by parenteral iron-related ADEs was lower than the actual number of ADEs. The average number of ADEs reported per patient was 3.6, 3.0 and 3.1 for Ferrlecit®, Dexferrum® and InFed®, respectively.

Relative frequency of ADEs by formulation

Table 1 shows the actual number of reported ADEs associated with each iron formulation. The latter two columns show the ORs and 95% CIs for each ADE comparing Ferrlecit® and Dexferrum® with InFed®. Total ADEs were significantly increased among recipients of higher molecular weight iron dextran (OR 5.5, 95% CI 4.9–6.0) and sodium ferric gluconate complex (OR 6.2, 95% CI 5.4–7.2) compared with lower molecular weight iron dextran. The odds of death associated with the use of higher molecular weight compared with lower molecular weight iron dextran was 3.6 (1.4–9.4). The risks of other specific ADEs (including life-threatening and non-life-threatening ADEs) were increased 2- to 12-fold in persons given higher molecular weight compared with lower molecular weight iron dextran. The risks of non-life threatening ADEs (including other allergic reactions, back pain, chest pain, dyspnoea and vomiting, among others) were increased 4- to 14-fold in persons given sodium ferric gluconate complex. In contrast, the risks of life-threatening ADEs (death, anaphylactoid reaction, cardiac arrest and respiratory depression) were not significantly different when comparing lower molecular weight iron dextran and sodium ferric gluconate complex, due in part to the low number of events. Figure 1 summarizes the overall serious ADE rate per million doses (normalized to 100 mg intravenous iron per dose).

Inclusion of non-specified ADEs

There were 221 iron dextran-related ADEs reported by generic name only and five iron gluconate-related ADEs reported by generic name only (including two deaths). If we were to assign all 221 iron-dextran-related ADEs to the low molecular weight iron dextran group (InFed®) group, we would not extinguish the increase in ADE risk associated with alternative formulations. Under these extreme assumptions, the OR and 95% CI for Dexferrum® for all ADEs would

Table 1. Major ADEs by parenteral iron formulation

ADE	Ferrlecit® ($n = 1\,083\,000$)	Dexferrum® ($n = 5\,058\,000$)	InFed® ($n = 14\,919\,000$)	OR Ferrlecit® *vs* InFed®	OR Dexferrum® *vs* InFed®
Death	1	11	9	1.5 (0.1–11.7)	3.6 (1.4–9.4)
Anaphylactoid reaction	3	14	28	1.5 (0.4–5.0)	1.5 (0.7–2.9)
Allergic reaction	7	4	13	7.4 (2.7–19.9)	0.9 (0.3–3.0)
Facial oedema	1	10	5	2.8 (0.1–23.9)	5.8 (1.9–19.7)
Pruritus	10	57	19	7.3 (3.1–16.4)	8.8 (5.1–15.4)
Urticaria	5	24	10	6.9 (2.1–21.8)	7.0 (3.2–15.7)
Back pain	15	94	23	9.0 (4.5–17.3)	12.1 (7.5–19.5)
Cardiac arrest	0	25	14	0 (0–5.1)	5.3 (2.6–10.7)
Chest pain	23	87	33	9.6 (5.5–13.8)	7.8 (5.5–11.8)
Tachycardia	2	24	10	2.8 (0.4–13.3)	7.0 (3.2–15.7)
Hypotension	23	72	35	9.1 (5.2–15.8)	6.1 (4.0–9.3)
Dyspnoea	18	107	57	4.4 (2.5–7.6)	5.5 (4.0–7.7)
Respiratory depression	0	13	7	0 (0–10.8)	2.3 (1.0–4.9)
Nausea	15	43	21	9.8 (4.8–19.9)	6.0 (3.5–10.5)
Vomiting	9	23	9	13.8 (5.0–37.7)	7.5 (3.3–17.4)
Sweating	5	32	9	7.7 (2.2–24.9)	10.5 (4.8–23.6)
Total	271	1112	598	6.2 (5.4–7.2)	5.5 (4.9–6.0)

Two additional deaths were reported in association with iron dextran (formulation unknown). If the additional deaths were associated with InFed®, the OR and 95% CI for Ferrlecit® *vs* InFed® would be 1.3 (0.1–9.3).

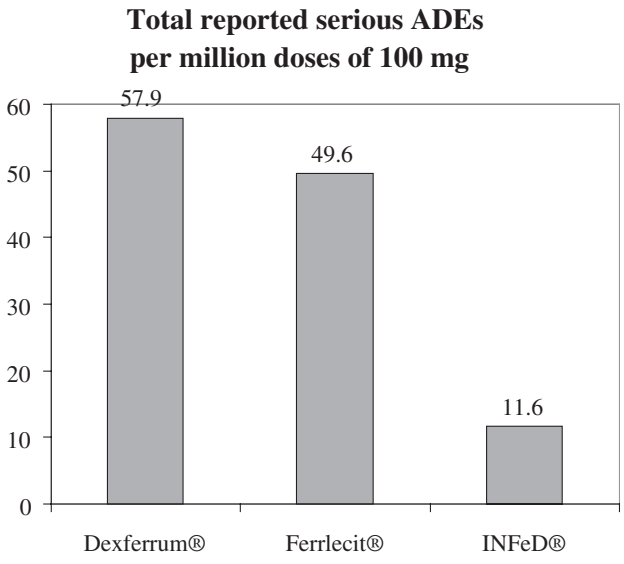

Fig. 1.

be reduced to 4.0 (3.7–4.3), and for Ferrlecit® to 4.6 (4.0–5.3).

Consideration of alternative vial size and total ADEs

The results outlined above normalize results per 100 mg iron equivalent. If one were to assume that Ferrlecit® were administered only in 62.5 mg increments, then the OR and 95% CI per dose (rather than per 100 mg) would be reduced from 6.2 (5.4–7.2) to 4.2 (3.6–4.9). If one were to assume that Ferrlecit were administered only in 125 mg increments, then the OR and 95% CI per dose would be increased to 7.8 (6.7–9.0).

Discussion

The efficacy of parenteral iron in supporting erythropoiesis is indisputable [1]. While several reports on the safety data of parenteral iron preparations have been published, the study designs and clinical settings have varied widely. Older studies included solely non-ESRD patients and many described ADEs with formulations of intravenous iron that are no longer commercially available [8]. Few studies have directly compared different formulations of parenteral iron until recently [9,10].

Fletes *et al.* [6] aimed to determine the incidence of iron dextran-related ADEs in clinical practice, and to attempt to characterize risk factors and describe outcomes associated with iron dextran-related ADEs. The authors identified 165 suspected ADEs among 841 252 intravenous iron dextran administrations during a 6-month study period, corresponding to an overall rate of 0.000196%, or ~20 per 100 000 doses. While some differences between the cases and the >85 000 patient cohort were statistically significant, the authors were unable to identify clinically significant differences in patient characteristics associated with iron dextran-related ADEs. A *post hoc* analysis revealed an 8-fold higher ADE rate associated with the use of the higher molecular weight iron dextran formulation (Dexferrum®) that could not be explained by differences in patient or facility characteristics.

McCarthy *et al.* [11] described iron dextran-related ADEs during 665 courses of parenteral iron dextran given to 254 patients over a 5-year period. The higher molecular weight iron dextran was associated with a significantly higher ADE rate than a lower molecular weight formulation, with rates of 11 out of 197 (5.6%) *vs* 10 out of 468 (2.1%) ($P = 0.02$). There were no differences in haemoglobin or serum

ferritin concentrations (i.e. efficacy) between the two groups.

More recently, Michael *et al.* [12] reported on the results of a placebo-controlled randomized trial using sodium ferric gluconate complex (Ferrlecit®) in haemodialysis patients. Overall event rates were extremely low. Compared with placebo, there was a significant increase in drug intolerance associated with Ferrlecit® administration (intolerance defined as an ADE precluding re-exposure). The authors reported a highly significant difference in ADE rates between iron dextran and sodium ferric gluconate complex (2.47 *vs* 0.44%, $P < 0.0001$). These findings led the authors to state that 'routine use of iron dextran in hemodialysis patients should be discontinued'.

A more careful examination of the control studies is warranted. Four studies were pooled in what the authors described as a meta-analysis, although no information was provided on study quality, heterogeneity or other factors that might indicate appropriateness for meta-analytic study. Hamstra *et al.* [8] reported on the frequency of life-threatening events occurring in 471 patients and 10 prisoners with iron deficiency, with or without other non-renal autoimmune or inflammatory diseases. This study used Imferon®, a high molecular weight iron dextran formulation that was recalled by the FDA in 1990, and soon after withdrawn from the market. The doses of iron dextran given in this study were typically in the 250–500 mg range. A second control formulation was Feridex®, an aqueous colloid of superparamagnetic iron oxide associated with dextran used as a radiocontrast medium (for magnetic resonance imaging) [13]. Feridex® has never been used therapeutically for correction of iron deficiency anaemia or in the context of ESRD. Indeed, publications describing the efficacy of Feridex in imaging have concentrated on persons with focal hepatic lesions (e.g. hepatocellular carcinoma, hepatic metastases) [14]. Faich and Strobos [15] refer to unpublished data from a 100-hospital network database, where the authors considered the simultaneous administration of iron dextran and intravenous epinephrine during hospitalization as an ADE. The authors provided no detail on the five alleged events, and failed to distinguish among different iron dextran formulations. The fourth control was a well-conducted open label trial of a lower molecular weight iron dextran formulation (InFed®) in 573 haemodialysis patients treated over a 2-year period [16]. Twenty-seven of 573 (4.7%) patients experienced ADEs, of which four (0.7%) were classified as serious (requiring hospitalization). While the ADE rate appears higher, the unit of evaluation was the patient, rather than a dose, as in the study of Michael *et al.* [12]. If one were to conservatively estimate the number of doses of iron dextran administered over 2 years at 20 per patient (providing 1 g of elemental iron per year, less than usual losses), then the overall ADE rate per dose of iron dextran would be 0.24%. The rate of iron dextran-related ADEs precluding re-exposure from the Fishbane *et al.* study was not calculated, but was probably <0.24%. In contrast, 3.9% of subjects who received a single dose of sodium ferric gluconate complex (Ferrlecit®) in the study of Michael *et al.* [12] experienced an ADE considered by the investigator to be possibly or probably related to the study drug, a value significantly higher than placebo (2.5%, $P = 0.0006$).

Multiple investigators have explored the associations among laboratory proxies of iron status and outcomes in the haemodialysis population, and have generally shown hyperferritinaemia to be associated with increased mortality and morbidity. Whether this association relates to iron overload or associated inflammation is unclear. Fewer epidemiological studies have focused on the provision of intravenous iron and associated outcomes. Feldman *et al.* [17] reported an 11% increase in the risk of death and 12% increase in the risk of hospitalization associated with the provision of >10 vials of intravenous iron over a 6-month period in a study of >5000 patients with ESRD in the USA. The formulations used in this study were not reported.

Immediate or short-term toxicities of iron have been attributed jointly to the effect of free iron on oxidative stress, and the relative protective and allergic effects of the carbohydrate shields (e.g. dextran, gluconate and sucrose). The most comprehensive experimental study in this area was published by Zager *et al.* [18] who compared three commercially available iron formulations (low molecular weight iron dextran and sodium ferric gluconate complex, described above, along with iron sucrose) and iron oligosaccharide, on *in vitro* proxies of oxidative injury. Briefly, all parenteral agents were pro-oxidant, although the relative effects of different formulations depended on the particular experimental model tested. While provocative, the experimental data available to date cannot explain the findings we have observed.

There are several important limitations to these analyses. We had no detailed clinical information on the patients treated with parenteral iron. We could not learn whether the patients treated had ESRD, CKD or other conditions associated with iron deficiency (e.g. blood loss due to menorrhagia) and inflammation (e.g. rheumatoid arthritis and other autoimmune diseases). However, patients on haemodialysis account for the vast majority of intravenous iron infused in the USA (A. J. Collins, personal communication). Confounding by indication or provider preference cannot be ruled out, but is unlikely to account for a multiple fold increase in the risk of parenteral iron-related ADEs. The differences between higher and lower molecular weight iron dextran formulations have been identified previously [6,11]. It is possible that clinicians may have been more vigilant with patients exposed to sodium ferric gluconate complex (Ferrlecit®) since this agent had not been widely used in ESRD, so that the fraction of cases reported may have been higher. However, a reporting bias is unlikely to explain the large observed inter-agent differences. Given the voluntary nature of ADE reporting, it is likely that all ADEs were

underascertained, especially more minor ADEs. Major ADEs, such as those listed in Table 1, would be more likely to be reported under any circumstances. We did not include data on iron sucrose, since it was rarely used during the time frame studied. These analyses should be updated after sufficient patient-years of iron sucrose exposure. Finally, the data used for the analyses were not derived from a randomized clinical trial. However, for exceptionally rare events such as serious parenteral iron-related ADEs, data from ongoing clinical practice may be more sound than data from clinical trials, since the power of clinical trials to detect rare but clinically important events is usually severely limited. These results highlight the importance of ongoing vigilance and active reporting of ADEs [19]. Lasser *et al*. [20] showed that >10% of drugs approved by the FDA between 1975 and 1999 either acquired a new black box warning, or were withdrawn from the market.

In summary, using data obtained from the FDA Medwatch programme, we demonstrated an increase in the risk of ADEs when comparing higher *vs* lower molecular weight iron dextran formulations, and when comparing sodium ferric gluconate complex with lower molecular weight iron dextran. While the absolute ADE risk was low, the magnitude of the increased risks exceeded what might be expected from confounding or reporting biases. Since large-scale, long-term clinical trials comparing various parenteral iron formulations may not be practical (due to limited power and great expense), these data may be used to guide clinical decision making. We identified no benefit and an increase in risk associated with higher molecular weight relative to lower molecular weight iron dextran. We were unable to confirm or refute the contention that non-dextran formulations of parenteral iron are associated with a reduced risk of death, anaphylactoid reactions, cardiac arrest or respiratory depression. Additional research will be required to determine the optimal formulation, dose and schedule of parenteral iron in haemodialysis patients.

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Conflict of interest statement. O.V.-N. is employed by Nebo a/s, a Danish company responsible for the marketing of CosmoFer®, a lower molecular weight iron dextran. O.V.-N. was included as a co-author of the manuscript with the unanimous approval of the other authors, because of his intellectual contributions. G.M.C. conducted the statistical analyses, and the authors collectively were responsible for data interpretation, without influence by O.V.-N. or any other employee or affiliate of Nebo a/s.

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