REVIEW ARTICLE

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Parenteral iron safety in haemodialysis patients

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ABSTRACT

Parenteral iron is a mainstay of anaemia management in end-stage renal disease patients undergoing haemodialysis. There are four parenteral iron formulations available with similar efficacy but the choice of the preferred formulation is not unanimous due to safety *versus* price concerns. Some characteristics of parenteral iron related adverse events, especially their rarity, impair the execution of studies with methodological consistency and, simultaneously, statistical power. Despite being more expensive, current guidelines recommend the use of non-dextran formulations (especially iron sucrose) due to the high incidence of adverse drug events registered with the first formulation available, high molecular weight iron dextran. However, current evidence demonstrates that the newer low molecular weight iron dextran has far fewer adverse drug events and so should be considered separately from high molecular weight iron dextran. We reviewed the evidence that compares the formulation unanimously considered the safest (iron sucrose) with low molecular weight iron dextran, which is cheaper and has an apparently acceptable safety profile. However, almost all published studies enrolled too few patients and were unable to reach statistically significant results. The first study that was able to find statistically significant differences was a pharmacovigilance database review which showed that iron sucrose had fewer reported total, life-threatening and fatal adverse drug events than low molecular weight iron dextran. These findings were further supported by a recent prospective randomised trial. The new iron formulations (ferric carboxymaltose and ferumoxytol) may represent the new generation of parenteral iron, but still need further validation in comparative studies with the existing formulations, especially iron sucrose.

Key-Words:
Anaemia; end-stage renal disease; haemodialysis; iron sucrose; low molecular weight iron dextran; parenteral iron safety.

INTRODUCTION

Iron deficiency is the main reason for hyporesponsiveness to erythropoiesis stimulating agents (ESAs) among end-stage renal disease (ESRD) patients. Some studies have demonstrated that a patient undergoing regular haemodialysis needs on average 1500 mg of iron per year to keep adequate iron stores[1]. Accidental blood losses through the vascular access, extracorporeal circuit coagulation, routine blood analysis, occult gastrointestinal bleeding and impaired absorption are some causes of chronic iron deficiency in these patients. Several studies in ESRD patients have shown that parenteral iron supplementation is far superior to oral supplementation, which is particularly ineffective[2]. Accordingly, parenteral iron is a mainstay of effective and cost-effective anaemia treatment in ESRD patients undergoing haemodialysis.

There are currently four parenteral iron formulations available: high molecular weight iron dextran

(HMWID), low molecular weight iron dextran (LMWID), ferric gluconate (FG) and iron sucrose (IS). Two drugs or two formulations of the same drug can be compared as to price, efficacy and safety. Concerning the price, in Europe FG is the most expensive, followed by IS and, finally, the iron dextran formulations. Several studies have demonstrated that all parenteral iron formulations are equally effective, with no significant differences between them[3] – all increase iron stores, improve haemoglobin, decrease ESA needs and, as a consequence, reduce costs. The remainder is parenteral iron safety. Several studies and contradictory opinion articles have been published on this subject, and the choice of the parenteral iron formulation in hospitals and haemodialysis units is not unanimous. The aim of this article is to review the existing evidence to determine which formulation presents the most favourable safety profile.

PARENTERAL IRON SAFETY

Parenteral iron safety can be divided into short-term and long-term safety. The latter is related to the increase of oxidative stress secondary to the increase in free iron resulting from parenteral iron administration. Iron oxidation is one of the main pathways for superoxide generation *in vivo* and, in theory, formulations with a stronger iron binding (such as the dextran formulations) would have lower oxidative potential. In fact, there are some studies, almost all *in vitro*, that show an increase in oxidative stress and transient renal alterations (< 24 hours) related to intravenous iron exposition[4-6]. These changes were more pronounced with non-dextran iron formulations. However these studies were conducted with iron concentrations far superior to the ones obtained *in vivo* and two observational studies did not show an increase in mortality with the use of parenteral iron[7,8]. Short-term safety is related mainly to allergic reactions (type I hypersensivity reactions) that occur either during or in the first hours after administration. Most published studies into parenteral iron safety report only immediate/short-term adverse drug events (ADE), and we will focus our attention on this subject.

The first parenteral iron formulation available, HMWID, had a high frequency of life-threatening ADE. Thirty-one deaths occurring in association with 196 cases of anaphylaxis were recorded in the United States between 1976 and 1996 related to HMWID administration[9]. Two retrospective studies estimated a 0.6 – 0.7% frequency of life-threatening ADE with HMWID[10,11]. As a consequence, the use of parenteral iron, particularly iron dextran, was cursed with an unsafe stigma.

However, in the last decade new formulations of parenteral iron with lower frequency of ADE became available – chronologically: LMWID, FG and IS. While several studies into their efficacy and safety have been published, few directly compare two or more formulations[12]. The characteristics of the ADE make it difficult to carry out studies with simultaneous methodological consistency and statistical power. Some of these characteristics are their reduced incidence (34 to 98 ADE/million administered doses)[13,14], the overlap with adverse events of other treatments (particularly haemodialysis), the subjectivity of evaluation and their occurrence almost always in the first administration. In a recently published systematic review it was calculated that to show a statistically significant difference for an increase in a serious ADE from 1% to 2% (between two forms of parenteral iron), with 90% power, in a randomised controlled trial, 3300 patients would be needed in both groups (i.e. a total of 6600 patients)[12]. Such a study has never been performed, and probably never will be.

What is the recommendation of the current guidelines?

The European Best Practice Guidelines (2004) consider IS the safest parenteral iron formulation, followed by FG, and do not recommend the use of iron dextran due to the risk of life-threatening ADE (Fig. 1) [15].

The NKF/KDOQI Guidelines (2006) only forewarn that in the case of iron dextran administration resuscitative medication and trained personnel should be present (Fig.2) [16].

In conclusion, current guidelines do not distinguish between the two iron dextran formulations and consider them less safe than the non-dextran formulations, particularly IS.

Guideline III.2 – Recommendation IV:

When selecting a source of supplementary iron, the tolerability profile of different sources of iron must be considered.

- **Iron sucrose** is generally considered to be the **safest** form of i.v. administered iron, followed by iron gluconate.
- Due to the risk of life-threatening/serious acute reactions associated with i.v. administration of **iron dextran**, this form of iron therapy **is not generally recommended**.
- If iron dextran is to be used, a **test dose** must be administered. In addition, special caution should be exercised in patients with multiple drug allergies/intolerance.

Evidence level B

Figure 1

European Best Practice Guidelines recommendations on use of parenteral iron.

III – Clinical practice guidelines and clinical practice recommendations for anemia in CKD in adults

3.2.6 – Using iron agents. Hypersensivity reactions.

In the opinion of the Work Group, resuscitative medication and personnel trained to evaluate and resuscitate anaphylaxis should be available whenever a dose of iron dextran is administered.

Figure 2

NKF/KDOQI Guidelines recommendations on use of parenteral iron.

HMWID vs. LMWID

Is the safety profile of HMWID and LMWID the same, as the currently existing guidelines seem to consider? The existing evidence tells us otherwise. At least six studies demonstrate that the frequency of ADE is far superior with HMWID than LMWID, with odds ratio between 3.2 and 8.1 (Table I).

LMWID vs. Iron Sucrose

For clinical purposes the really important comparison to make is between the formulation unanimously considered the safest – iron sucrose – and the one which is cheaper and has an apparently acceptable safety profile – LMWID. There are so far six published studies comparing the two formulations – one systematic review[12], three observational studies[3,14,21] and only two prospective randomised controlled trials[22].

The systematic review included all studies with more than 10 patients published between 1990 and 2004 that evaluated the frequency of ADE of at least one of the two formulations. Sixty studies were included; however only 10 directly compared two parenteral iron formulations and of these only 2 compared LMWID with IS. This was the study that analysed the highest number of administered doses but due to the great heterogeneity of the studies the authors were unable to clarify which formulation is the safest, concluding only that the frequency of ADE is very low with both of them. In their conclusions the authors report that using large pharmacovigilance databases is the easiest way to find a concrete answer.

Three of the remaining studies, (two observational and one prospective randomised controlled

Table I

Comparison of HMWID and LMWID ADE frequency.

Study name	ADE Frequency	Study design
Chertow *et al.* Nephrol Dial Transplant, 2005.[14]	**Total ADE:** HMWID › LMWID (OR: 3.2) **Serious ADE:** FDAPM › FDBPM (OR: 3.4)	Retrospective. Review of the Food and Drug Administration (USA) database.
Chertow *et al.* Nephrol Dial Transplant 2004.[13]	HMWID › LMWID (OR: 5.5)	Retrospective. Review of the Food and Drug Administration (USA) database.
Fletes *et al.* Am J Kidney Dis 2001.[17]	HMWID › LMWID (OR: 8.12)	Retrospective. Review of the Fresenius Medical Care USA database.
McCarthy *et al.* Am JNephrol 2000.[18]	HMWID › LMWID (OR: 3.0)	Retrospective case review (Mayo Clinic).
Peck *et al.* J Pediatric Gastroenterology and Nutrition, 1998.[19]	HMWID (74%) › LMWID (9%)	Small prospective uncontroled trial in children with IBS.
Case G. ANNA J 1998.[20]	HMWID (28,6%) › LMWID (3,5%)	Small retrospective case review in home dialysis patients.

Table II

Small studies comparing ADE frequency of IS and LMWID.

Study	Design	Results	Conclusions	Limitations
Moniem and Bhandari. J Am Soc Nephrol, 2003[3]	Prospective. N=39 6 months HMWID → 6 months IS	**IS:** 5/507 ADE/dose (0.009%); 4/39 ADE/patient **FDBPM:** 8/546 ADE/dose (0.014%). No serious ADE or anaphylaxis detected. Saving of 77£/ patient / 6 months with LMWID.	Differences not statistically significant.	Small sample. Not randomised.
Prakash *et al.* Perironeal Dialysis International 2001[21]	Retrospective. N=56 (33 iron dextran; 23 IS)	**ID:** ADE in 14.7% of patients. 7.4% of doses. 1 serious ADE. No deaths. **IS:** ADE in 8.7% of patients. 4.3% of doses. 1 serious. No deaths.	Differences not statistically significant.	Small sample. Not randomised. Type of iron dextran not specified.
Tansu Sav *et al.* Renal Failure 2007[22]	Prospective, randomised, double blind. 2 groups (n = 30/group); group 1: IS, group 2: LMWID; 5 months. Patients not previously exposed to parenteral iron and no history of atopy.	**LMWID:** ADE in 11/30 patients **SF:** ADE in 13/30 patients No life-threatening ADE.	Differences not statistically significant.	Small sample.

trial) had small sample sizes (40 to 60 patients) and were unable to find statistically significant differences between the two parenteral iron formulations (Table II). However, the frequency of ADE appears to be low with both formulations.

The first study that was able to establish statistically significant differences between the two parenteral iron formulations was published by G. Chertow *et al.*[14] in 2005. This is a review of the Food and Drug Administration (USA) pharmacovigilance database comparing the frequency of ADE of the four available parenteral iron formulations reported over three years (2001 -2003). The global frequency of ADE was very low (approximately 38 ADE/million doses). Eleven deaths, assumed to be iron-related, occurred in more than 30 million administered doses, with at least one related to each parenteral iron formulation. Concerning the relative frequency of ADE it was demonstrated that IS has a better safety profile than LMWID and the difference between LMWID and HMWID was confirmed again (Table III).

Iron sucrose had a lower frequency of reported total, life-threatening and fatal ADE than LMWID, with the differences statistically significant. The results of this study revealed a frequency of life-threatening ADE of 0.6/million administered doses for IS, 0.9/million administered doses for FG, 3.3/million administered doses for LMWID and 11.3/million administered doses HMWID.

Table III

Relative frequency of ADE (adapted, with permission, from Chertow *et al*; NDT; 2005)

Adverse Drug Event	Odds ratio HMWID *vs.* LMWID	Odds ratio IS *vs.* LMWID
Death	1.0 (0.2 – 4.6)	0.2 (0.1 – 1)
Cardiac arrest	4.2 (1.4 – 12)	0.0 (0.0 – 0.6)
Coma	5.7 (2.2 -14)	0.5 (0.2 – 1.7)
Anaphylactic reaction	2.6 (0.9 – 7.7)	0.0 (0.0 – 0.5)
Dyspnoea	4.1 (2.6 – 6.6)	0.3 (0.1 -0.5)
Allergic reaction	2.4 (1.4 – 4.2)	0.5 (0.3 -1.0)
Abdominal pain	1.7 (0.3 – 8.7)	1.3 (0.3 – 4.8)
Back pain	9.1 (4.2 – 20)	0.3 (0.1 -1.0)
Chest pain	5.2 (2.9 – 9.4)	0.4 (0.2 -0.9)
Hypotension	5.7 (2.9 – 11)	0.8 (0.3 -1.7)
Nausea	2.1 (0.9 – 5.1)	0.8 (0.3 -1.8)
Vomiting	2.4 (0.8 – 6.3)	0.3 (0.1 -1.2)
Sweating	9.8 (3.4 – 28)	0.6 (0.1 -2.3)
Total	3.2 (2.7 – 3.8)	0.5 (0.4 -0.6)
Life-threatening	3.4 (2.0 – 5.9)	0.2 (0.1 -0.4)

Extrapolating the results of this study for the Portuguese picture, for around 9000 patients on haemodialysis[23], one life-threatening ADE every 2.2 years and one fatality every 10 years could be expected if only LMWID was used, whereas if only IS was administered the estimation would be one life-threatening ADE approximately every 12.5 years and one fatality every 67 years (Table IV).

However, some of the limitations of this study should be pointed out. Most of them are related to

Table IV

Safety of IS *vs.* LMWID

	Iron Sucrose	LMWID
Life-threatening ADE risk/year[a]	0.08	0.45
Death risk/year[a]	0.015	0.1

a) Assuming that all patients would receive one of the parenteral iron formulations, with approximately 135.000 100mg doses/year (1500 mg/year/patient) administered

it being a study based on a pharmacovigilance system – the voluntary and subjective nature of the notification, the Weber effect (new substances are overnotified), the influence of pharmaceutical industry marketing and the complete absence of clinical information. In addition, the presentation of results per dose administered and not per patient, the elimination of a significant percentage of notifications because the type of iron dextran was not specified and, finally, the uncertainty about the number of doses effectively administered (the denominator used was the total number of dispensed doses which does not correspond necessarily to the doses actually administered), also lead to loss of precision.

Finally, this year G. Anirban and colleagues published a medium-sized single-centre, prospective randomised trial, comparing the safety of three parenteral iron formulations (LMWID, FG and IS)[24]. The study enrolled 339 patients and a total of 2980 doses were administered. As noted previously the global frequency of ADE was low (1.88% per infusion and 14.45% per patient) and no parenteral iron related deaths were registered. Serious ADE (anaphylactic or suspected immune-allergic events) were seen in 6.2%, 1.8% and 0.9% of infusions with LMWID, FG and IS, respectively. Statistically significant differences in the frequency of serious ADE per patient (OR 7.6; p=0.034) and per infusion (OR 7.8; p<0.001) were found between LMWID and IS. Probably due to the relatively small sample size no deaths were recorded and so no differences were established. As stated before, this study is still far from the over 6000 patients needed for establishing statistically significant differences and recording rare events, and it could be argued that the results were a matter of chance. Although still underpowered, this study confirmed what had already been demonstrated in the large retrospective pharmacovigilance database analysis discussed above, which in part accounts for the reliability of the results obtained.

In Portugal there are two IS formulations available, including a generic formulation. It is worth emphasising that almost all the reviewed studies (namely the G. Chertow large pharmacovigilance database review) were conducted with the original molecules of each iron formulation. An experimental study in rats using intravenous iron doses well above the recommended dosage in humans (40mg/kg/week) suggests that the generic formulation is associated with higher oxidative stress, inflammation and tissue damage, which would result from slight differences in chemical characteristics[25]. These concerns should be assessed in clinical studies with the iron dosage currently used.

New parenteral iron formulations

Each of the currently available parenteral iron formulations has safety and/or convenience limitations. The latter is especially relevant in CKD patients not on dialysis since the non-dextran iron formulations can only be administered in relatively small doses and multiple administrations must be scheduled.

Two new parenteral iron formulations – ferric carboxymaltose and ferumoxytol – have been developed and are currently undergoing Phase III clinical trials. The potential advantages of these new formulations is the possibility of administering larger doses (up to 1000mg of iron), as is already possible with LMWID, in short periods of time without compromising efficacy, safety and tolerability, as suggested by some recent studies[26-29]. In the case of ferric carboxymaltose, these advantages would come from a different carbohydrate shell and higher molecular weight (intermediate between IS and LMWID), which account for a distinct release pattern causing less oxidative stress, as suggested by experimental and preclinical studies[30].

However, clinical data on safety of the new formulations are still scarce and come not from safety oriented studies but from secondary endpoints of efficacy studies. More importantly comparative studies (of efficacy and safety) between the new parenteral iron formulations and the currently existing ones still need to be performed before premature conclusions are drawn. The few currently published studies (almost all of them with ferric carboxymaltose) compare the new formulations only with oral iron, in various disease states[31-35]. Nevertheless, these new formulations represent an exciting new pathway for investigation in parenteral iron therapy.

CONCLUSIONS

Adverse drug events with the parenteral iron formulations currently available are rare, particularly life-threatening ADE. Comparative studies between different formulations are very few and the existing ones are either small or subject to important bias. Ideally, large prospective, randomised, double blind, controlled trials should be carried out to compare parenteral iron formulations. In the absence of such studies, reviews of large databases remain the best tool to detect rare events and compare two formulations. The only study using this methodology, directly comparing IS with LMWID, revealed statistically significant differences in the incidence of total, life-threatening and fatal ADE. These results were recently supported by a medium-sized prospective randomised trial, with the exception of fatal ADE. The actual safety profile of IS, regardless of price, is probably the explanation for the wide use of IS instead of LMWID in Portugal.

The new parenteral iron formulations may represent the beginning of a new era in intravenous iron therapy, however work still needs to be done to determine the comparative efficacy and toxicity profile of the currently existing formulations.

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