Intravenous iron therapy: how far have we come?

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Oral iron supplementation is usually the first choice for the treatment of iron deficiency anemia (IDA) because of its effectiveness and low cost. But unfortunately in many iron deficient conditions, oral iron is a less than the ideal treatment mainly because of adverse events related to the gastrointestinal tract as well as the long course required to treat anemia and replenish body iron stores. The first iron product for intravenous use was high-molecular-weight iron dextran. However, dextran-containing intravenous iron preparations are associated with an elevated risk of anaphylactic reactions, which made physicians reluctant to prescribe intravenous iron in the treatment of iron deficiency anemia for many years. In 1999 and 2001, two new intravenous iron preparations (ferric gluconate and iron sucrose) were introduced into the market as safer alternatives to iron dextran. Over the last five years, three new intravenous iron dextran-free preparations have been developed and have better safety profiles than the more traditional intravenous compounds, as none require test doses and all these products are promising in respect to a more rapid replacement of body iron stores (15-60 minutes/infusion) as they can be given at higher doses (from 500 mg to more than 1000 mg/infusion). The purpose of this review is to discuss some pertinent issues in relation to the history, pharmacology, administration, efficacy, safety profile and toxicity of intravenous iron for the treatment of iron deficiency anemia.

Keywords: *Iron deficiency; Anemia, iron-deficiency; Iron compounds; Infusions, intravenous*

Introduction

Iron is an essential element as it plays an important role in many vital biological processes such as the synthesis of heme which forms the basis of hemoglobin (Hb) the oxygen-carrying protein of the blood, the formation of myoglobin, energy metabolism, neurotransmitter production, the formation of collagen and immune system function.[1,2] Lack of iron is one of the principal causes of anemia in the general population. It is not surprising that iron deficiency anemia (IDA) is associated with increased morbidity and mortality.[2,3]

Iron has been used to treat anemia for more than 300 years. However, it was not until the 19th century when Pierre Blaud introduced ferrous sulfate that it became the standard treatment for IDA.[4]

Treatment with oral iron supplements is simple, inexpensive and a relatively effective way of treating iron deficiency conditions. Ferrous iron salts (sulfate, fumarate, succinate and gluconate) are the most commonly used oral iron preparations; they are similar in regards to pharmacodynamic and pharmacokinetic properties as well as to the rate of adverse events (AEs).[5-8]

Because of the high rate of gastrointestinal AEs (35% to 59%) with ferrous sulfate, new compounds containing either the ferric or ferrous salt forms have been developed as different preparations (amino-acid chelates, carbonyl iron, iron III polymaltose complex [IPC], extended-release products) and approved for clinical use.[5-8] Among these preparations, IPC is the most studied and used to treat IDA patients; it is not affected by food, milk or medicines which permits its ingestion during or after meals and the tolerability of IPC has proved to be much better, leading to higher compliance rates and improved effectiveness compared to ferrous sulfate.[9-12]

For the treatment of IDA in adults, the recommended daily dose of elemental iron is in the range of 150 to 200 mg/day; for children the dose is 3-6 mg iron/Kg body weight/day. From a practical point of view, doses of 100-200 mg/day of elemental iron are a compromise between the optimum Hb increase and body iron replenishment with minimal AEs. However, some studies have shown that smaller daily doses of elemental iron may be adequate to prevent iron deficiency and can also correct IDA without producing substantial AEs.[7,13]

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Successful overall management of the patient with IDA must include attempts to identify and treat, if possible, the underlying cause(s) of the iron deficiency. Response to oral iron is highly predictable under uncomplicated circumstances, particularly in the absence of inflammation and significant ongoing blood loss. In other words, very few patients will fail to respond to oral iron salts provided significant doses can be tolerated.[5-8] If response does not occur within 3-4 weeks of appropriated treatment, there is no reason to continue the treatment further, rather an explanation for failure should be sought.

On the other hand, it is very well known that oral iron is a less than ideal treatment mainly because of gastrointestinal AEs (particularly when using ferrous iron compounds), lack of adherence to therapy or insufficient length of therapy for the degree of iron deficiency, poor duodenal absorption due to concomitant gastrointestinal pathologies (inflammatory bowel disease [IBD] or any other cause of chronic inflammation, malignancy) and the long course of treatment needed to resolve anemia (1-2 months) and replenish body iron stores (another 3-6 months). Noncompliance to a prescribed course of oral iron is common and even in compliant patients, poor intestinal absorption fails to compensate for the iron need in the presence of ongoing blood losses or in inflammatory conditions.[5,7,8]

In addition to that, adequate iron stores are essential to achieve maximum benefit from erythropoiesis-stimulating agents (ESAs). Decreased iron stores or decreased availability of iron are the most common reasons for resistance to the effect of these agents. Thus, oral iron therapy should not be considered for chronic kidney disease (CKD), patients on hemodialysis and cancer patients receiving ESAs because of the inflammatory state. In this scenario, oral iron is poorly absorbed from the intestinal tract due to upregulation of hepcidin, a peptide hormone that plays a central role in iron homeostasis.[14] In addition to this, in IBD, the possibility that iron may further damage the intestinal mucosa should be a serious indication for the use of IV rather than oral iron therapy.[15-20]

Intravenous iron therapy

Treatment with IV iron is clearly superior to oral iron and presents several advantages such as faster and higher increase in Hb levels and replenishment of body iron stores. For these reasons, modern formulations of IV iron have emerged as safe and effective alternatives for IDA management.[15-20] The main clinical indications for IV iron treatment are listed in Table 1.

Intravenous iron: history, administration, efficacy, and safety

The ferric hydroxide preparation was the first iron compound for parenteral use introduced early in the 20th century. However, the lack of a carbohydrate shell of this compound resulted in immediate iron release and severe toxic reactions, which led to it being recommended only in extraordinary circumstances.[3]

Table 1 - Main clinical indications for IV iron treatment

1. Intolerance to oral iron or non-compliance to an oral regimen	
2. In acquired or hereditary decreased intestinal iron absorption and/or liberation of iron macrophages	Intestinal malabsorption syndromes*, inflammatory diseases (IBD), after gastrectomy/bariatric surgery, IRIDA
3. In cases with severe IDA (Hb < 9 g/dL) because of continuous or uncontrolled blood loss and/or because of increased iron needs	Hereditary hemorrhagic telangiectasias (Osler-Weber-Rendu disease), angiodysplasia due to other causes; pregnancy#, post-partum anemia; patients scheduled for surgery
4. In cases of functional iron deficiency particularly when an ESA is used	Anemia of chronic kidney disease, inflammatory diseases, anemia of cancer
5. Other circumstances	Autologous blood donation before elective surgery, Jehovah's Witnesses

* intestinal malabsorption can be detected by observing an increase in serum iron of less than 100 µg % over baseline in a fasting patient 1 or 2 hours after taking 60 mg iron as ferrous sulphate; IBD = inflammatory bowel disease; IRIDA = iron-refractory iron deficiency anemias; #beyond 14 weeks of pregnancy

The first high-molecular-weight iron dextran [HMW-ID]) for intramuscular and IV use (Imferon) was introduced in 1954.[21] HMW-ID consists of an iron oxyhydroxide core, which is surrounded by a carbohydrate shell made of polymers of dextran. This carbohydrate shell controls the release of free iron from the complex and also limits the total dose that can be given at any one administration. The bioavailability of iron occurs via uptake of iron dextran particles into the reticuloendothelial system (RES) with subsequent breakdown.[3,21]

However, the increased incidence of serious AEs reported with HMW-ID, particularly the well-know dextran-induced anaphylactic reactions, led to its recommendation only when extreme clinical conditions were present and other options unavailable. Although the exact mechanism of these AEs to iron dextran has not been clarified yet, it seems to be related to the antibody-mediated release of mediators by mast cells.[22,23]

HMW-ID was the only parenteral iron product available until 1989, when the first recombinant human erythropoietin (epoetin alfa) was introduced for clinical use.[3] Taking into consideration the importance of iron in erythropoiesis and that the most common reason for ESA treatment failure was shown to be due to absolute or functional iron deficiency[24] as the administration of IV iron restored responsiveness,[25] IV iron therapy has an essential role in achieving and maintaining target Hb levels in CKD patients, particularly as an adjunct to ESA therapy.

In 1992 and 1996 two new compounds INFeD® containing low-molecular-weight iron dextran (LMW-ID) and

Dexferrum® with HMW-ID, respectively; were approved by the Food and Drug Administration (FDA) for clinical use in the United States. These formulations can be administered as an IV bolus or total dose infusion (TDI) with doses up to 1000 mg. Both of them required a test dose and had black box warnings.[3]

In a retrospective review of more than 30 million doses of IV iron, Chertow et al.[26] showed that the use of LMW-ID was associated with a lower risk of AEs compared to HMW-ID compounds. Moreover, only a history of allergies predicted otherwise very infrequent AEs.[27]

Nevertheless, HMW-ID is not commercially available in Europe, the National Comprehensive Cancer Network recommends against its use and the FDA has altered HMW-ID (Dexferrum®) labeling to warn that it is not clinically interchangeable with LMW-ID (INFeD®).[14,28]

In 1999, ferric gluconate (FG) (Ferrlecit), after having been available in Europe for many years, was introduced into the American market as a safer alternative to iron dextran.[3]

A historical review of the use of FG in Europe and iron dextrans in the United States found no deaths attributable to FG, but at least 31 to iron dextran. The authors concluded that FG was a safer therapeutic option to iron dextran and its safety was related to the lack of the dextran envelope and therefore associated with a lower risk of anaphylactoid reactions.[29]

The maximum recommended dose of FG is 125 mg given as a bolus or short infusion; it has been reported that an infusion of 250 mg given over 1 hour is safe.[30]

A double-blind, placebo-controlled crossover study of single dose administration of FG in 2338 hemodialysis patients reported only one serious allergic reaction and no deaths.[30,31] They further reported that, in patients previously sensitive to iron dextran, reactions to FG were uncommon, but 7-fold more common than those without prior iron sensitivities.[30]

In November 2000, iron sucrose (IS) (Venofer) was approved in the United States although it had also been used for a long time in Europe. By far, the greatest experience in published literature is with this formulation.[3]

IS can be safety administered as a 15-30 minute infusion in doses of 200-300 mg; the maximum weekly dose should not exceed 600 mg. If higher-than-recommended doses are not infused, AEs are rarely observed.[18,32,33]

IS is a dextran-free formulation with a safety profile similar to FG.[32] The efficacy and safety of IV IS has been shown in the treatment of anemia including in CKD patients on hemodialysis.[34,35] Furthermore, IS is also effective in the treatment of IDA patients combined with IBD, whereas oral iron is potentially harmful to the intestinal epithelium.[36] It has been shown that IS is an important alternative option to blood transfusion in a variety of surgery settings leading to significant reduction of blood transfusion requirements.[37-41]

The incidence of serious life-threatening anaphylaxis with IS is 0.002% *versus* 0.6-2.3% and 0.04% with HMW-ID and FG, respectively. Moreover, fatal hypersensitivity reactions have not been reported with IS. When doses higher than 250 mg of FG or 300 mg of IS are administered, infusion reactions occur probably due to free iron release from the less tightly bound carbohydrate carriers.[26-29] Black box warnings do not appear in the directions for use of either FG or IS and a test dose is not required.

Based on the current state of knowledge, FG and IS largely replaced the use of iron dextrans in US patients.[3]

In despite of being the most frequently used IV iron compound in published studies, the main disadvantage of IS is the need for multiple infusions as the maximum weekly dose should not exceed 600 mg (200 mg IV, 1-3 times/week).[3,42]

These restrictive and time-consuming administration requirements may contribute to the underuse of IV iron in the treatment of IDA. Consequently, there was a clear need for a cost-effective IV iron therapy with favorable administration regimen that could potentially help to increase its use and improve outcomes.[3,18,21,42]

Newer intravenous iron formulations

In the last 2 years, three new IV iron compounds have been released for clinical use in patients with IDA. Two are currently approved for use in Europe [ferric carboxymaltose (FCM)[21,43-47] and iron isomaltoside 1000 (Monofer®)][48] and one in the United States [Ferumoxytol (FeraHeme®)].[49-51]

In their pre-registration trials, all of these three new compounds potentially had better safety profiles than the more traditional IV preparations, particularly because these products may be given more rapidly and in larger doses than their predecessors with the possibility of complete replacement of iron in 15-60 minutes.

Ferric carboxymaltose (FCM)

FCM is a new parenteral dextran-free iron product and the first of the new agents approved for rapid and high-dose replenishment of depleted iron stores.[27]

FCM is an iron complex that consists of a ferric hydroxide core stabilized by a carbohydrate shell. The design of the macromolecular ferric hydroxide carbohydrate complex allows controlled delivery of iron to the cells of the RES and subsequent delivery to the iron-binding proteins, ferritin and transferrin, with minimal risk of releasing large amounts of ionic iron into the serum.[27]

FCM is a stable complex with the advantage of being non-dextran-containing and with a very low immunogenic potential and therefore the risk of anaphylatic reactions is low. Its properties permit the administration of large doses (15 mg/kg; maximum of 1000 mg/infusion) in a single and rapid (15-minute) infusion without the requirement of a test dose.[43-46]

The therapeutic efficacy of IV FCM has been evaluated in several randomized, open-label, controlled, multicentre trials

under different conditions associated with absolute or functional iron deficiency with or without anemia, including patients with IBD, heavy uterine bleeding, postpartum IDA, chronic heart failure and CKD patients on hemodialysis or not. Most of these trials compared FCM with oral iron and found it to have a better efficacy in terms of improving Hb levels and particularly with regards to the body iron replenishment; it was significantly faster and higher than with ferrous sulfate.[3,21,43-46]

Regarding the tolerability and safety profile, clinical trials of FCM evaluated 9312 patients (5638 in the FCM group and 3674 patients in a pooled control group); most drug-related AEs were considered transient and mild to moderate in intensity. Treatment was not permanently discontinued for any patient due to AEs. These studies concluded that FCM is well tolerated and has a clinically manageable safety profile when appropriate dosing and monitoring is used.[3,21,43-46]

FCM is approved in Europe, Asia, and Australia, but has not yet been approved by the FDA due to unexplained hypophosphatemia two weeks after infusion in patients with CKD and an imbalance in cardiovascular events and deaths in the treatment compared to the placebo arm. (http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4337b1-01-fda.pdf). However, it should be noted that none of the deaths in the submitted data were considered related to the administration of this IV iron.

The benefit of FCM is the efficacy of IV iron administration without the inconvenience of multiple small-dose injections and long infusion times. For example, if a patient requires 1000 mg of IV iron to correct the iron deficiency, this can be administered 20 times more rapidly with FCM than with iron dextran (0.25 hours versus 2.7 hours). The administration time for 1000 mg of FCM is 15 min in one visit compared with 161 minutes needed for IS administration. The resulting efficiency ratio is over 10 times better for FCM versus IS.[3,21]

Moreover, FCM effectiveness is associated with real cost-saving benefits for hospitals, healthcare providers and patients (less frequent and shorter hospital visits). [3,17,43-47] Based on Swiss structure of rates for medical services, the drug and administration costs for 1000 mg of IV iron are 137 • and 233 • (total of 370 •) for the use of IS, respectively and 250 • and 20 • (total of 270 •) for the use of ferric carboxymaltose, respectively.[47]

Ferumoxytol (FeraHeme®)

This formulation was approved by the FDA in 2009 for iron replenishment in CKD patients with IDA. It can be administrated as a relatively large dose (max 510 mg) in a rapid (< 20 seconds) session without test dose requirement.[49-51]

The published safety profile of ferumoxytol is consistent with that of LMW-ID, FG and IS. However, this product is not currently approved in Europe and the FDA is continuing to evaluate Ferumoxytol due to reports of serious cardiac disorders (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm223734.htm).

In addition, ferumoxytol administration may transiently interfere with diagnostic ability of magnetic resonance imaging which is frequently used for the diagnosis and follow-up of IBD; consequently this does not seem to be an appropriate IV iron compound for IBD patients. A warning about potentially life threatening events was added to the instructions for use of ferumoxytol in a recently mandated change.

Iron isomaltoside 1000 (Monofer®)

The newest IV iron agent, iron isomaltoside 1000 (Monofer®), was introduced into Europe in 2010. This formulation is a non-branched, non-anaphylactic carbohydrate, structurally different from the branched polysaccharides used in iron dextran.[48]

Iron isomaltoside 1000 has a very low immunogenic potential and a very low content of free iron and can therefore be administered as a rapid high dose infusion of up to 2000 mg without the application of a test dose, which offers considerable dose flexibility, including the possibility of providing full iron repletion in a single infusion (one-dose iron repletion).[49]

Most IV iron agents are colloids with spheroidal iron-carbohydrate nanoparticles. Each particle consists of a carbohydrate shell that stabilizes the iron-oxyhydroxide core (Fe [III]). However, the structure of Monofer® is somehow different, as the linear oligosaccharide isomaltoside 1000 allows the formation of a matrix with interchanging iron and carbohydrate, instead of a classical spheroidal iron carbohydrate nanoparticle.[49]

The availability of stable parenteral iron compounds allowing for higher dose infusion may greatly facilitate iron replacement therapy in IDA patients. The use of these stable compounds carries benefits for both the patient (less disruption of life, less time away from home/work, reduced injections, few side effects, etc.) and the hospital/health service (reduced visits, reduced physician and nurse time, improved out-patient management, improved cost-effectiveness, etc.). Other benefits of high dose or TID (three times daily) infusions are the significant reduction of treatment period[24] and the higher ferritin obtained,[43,52,53] which may be important to delay the recurrence of IDA.

Functional iron deficiency and intravenous iron therapy

In addition to absolute iron deficiency, it is now recognized that many patients may have functional iron deficiency. This is characterized by the presence of adequate

iron stores as defined by conventional criteria but an inability to sufficiently mobilize this iron, particularly when erythropoiesis is stimulated by an ESA.

The superiority of higher IV iron doses in patients with IBD has been reported by Evstatiev et al.[54] in a comparative clinical trial on the efficacy and safety of standardized FCM doses with respect to individually calculated IS doses. At week 12 after the initiation of iron therapy, the response rate (defined as an increase in hemoglobin levels of > 2 g/dL; 66.1% *versus* 54.1%), the proportion of non-anemic patients (72.8% *versus* 61.8%) and full compliance to the treatment regimen (92.5% *versus* 79.1%) were all significantly higher in the FCM group than in the IS group. In addition, there was no significant difference in treatment-related AEs between the two groups (13.9% *versus* 11.3%).

These results endorse the use of high dose infusion regimens and may explain the benefit of administering high doses of IV iron for iron deficiency in patients with inflammation (faster and more complete response).

But, what is the underlying mechanism? It is postulated that the marrow requires 20-30 mg/day for erythropoiesis. In these patients, a small proportion of the infused iron is delivered in the ferric form into the plasma and taken up by transferrin. According to data from *in vitro* studies, approximately 45 mg of iron can be sustained in the plasma after the administration of 1000 mg IV iron. Meanwhile, most of the administered iron dose is taken up by the macrophages. The iron overload of the macrophages in the RES may cause a 'by-pass' of the hepcidin block by over-expressing ferroportin and allowing a flow to the bone marrow, transported by transferrin (increased transferring saturation), to sustain erythropoiesis. In addition, in autoimmune diseases, macrophage iron loading may inhibit pro-inflammatory immune effector pathways, thus reducing disease activity (anti-inflammatory effect).[55]

Intravenous iron classification

IV iron complexes can generally be classified as labile or robust (kinetic variability) and as week or strong (thermodynamic variability) with all possible intermediates. Each iron-carbohydrate complex enters the RES macrophages of the liver, spleen, and bone marrow where the shell is broken down and the iron is released from the complex. The released iron is either transported into storage pools or is transported via plasma transferrin for its incorporation into Hb. Some characteristics of the different IV iron formulations are summarized in Table 2.[56]

Potential negative effects of intravenous iron

Many *in vitro* and *in vivo* studies have demonstrated a variety of AEs associated with iron, such as cytotoxicity, renal tubular damage, alterations in neutrophil function, promotion of atherosclerosis, promotion of tumor growth when used in patients with cancer and the generation of free radicals. Markers of oxidative stress have also been shown in humans, although they are predominantly limited to hemodialysis, since this is the most highly studied population.[3]

Current information on the relationship between IV iron and infection and between IV iron and oxidative stress deserves special consideration.

Iron is a pro-oxidant, an important nutrient for many bacteria, and in laboratory animals has been shown to exacerbate sepsis. Whereas human studies have shown transient increases in markers of oxidative stress with all forms of IV iron, no clinically negative outcomes associated with the increase in these markers have ever been reported.[57]

Elemental iron is an essential growth factor for bacteria with many species expressing iron transport proteins that compete with transferrin; it has long been suggested that patients with iron overload are at increased risk of infection.[58] In contrast, in the peritoneal dialysis population, no increased risk of peritonitis was found in patients receiving IV iron compared to those who did not receive.[59] In addition, a meta-analysis of 6 observational studies (807 patients) revealed that the administration of IV iron to patients undergoing major orthopedic surgery led to a significant decrease in both transfusion rate (RR: 0.60; 95% confidence interval [CI]: 0.50 - 0.72; p-value < 0.001) and infection rate (RR: 0.45; 95% CI: 0.32 - 0.63; p-value < 0.001).[60] Despite the absence of definitive clinical data, it seems sensible to avoid IV iron administration in the setting of acute infection, and to withhold IV iron in patients with pre-treatment ferritin values > 500 ng/mL.[38] Conversely, evidence available on IV iron administration in atherogenesis is indirect and there is little evidence that IV iron adversely affects survival in patients with dialysis-dependent CKD. On the other hand, IV iron therapy has not been associated with an increase in tumor incidence.[61] Nevertheless, the evidence demands caution, not complacency, in prescribing IV iron.[62]

The nature of a possible relationship between iron and cancer progression is unclear. Some studies suggest that iron overload could promote tumor growth through the catalytic effect of labile iron with the formation of hydroxyl radicals, its role in cell growth and angiogenesis. In general, preclinical models of iron overload do not reflect the clinical setting of IV iron therapy that attempts to restore a normal iron status in iron-deficient or anemic patients with cancer.[63-65]

The risk, if any, of IV iron causing infection and related morbidity and mortality is probably very small. Clinicians should weigh this information with the well-established benefits of effective iron management and anemia correction, including decreased morbidity and improved quality of life.[3]

Is premedication prior to intravenous iron therapy necessary: if yes, when and how?

Table 2 - Some characteristics of the different intravenous iron formulations

	Iron gluconate	Iron sucrose	Low-molecular-weight iron dextran	Ferric carboxymaltose	Iron isomaltoside 1000	High-molecular-weight iron dextran	Ferumoxytol
Brand name	Ferrlecit®	Venofer®	Cosmofer® INFeD®	Ferinject® Injectafer®	Monofer®	Dexferrum®	FeraHeme®
Carbohydrate shell	Gluconate (monosaccharide)	Sucrose (disaccharide)	Dextran (branched polysaccharide	Carboxymaltose (branched polysaccharide	Isomaltoside (linear oligosaccharide)	Dextran (branched polysaccharide)	Polyglucose sorbitol carboxymethyl-ether
Complex type	Type III Labile and weak	Type II Semi-robust and moderately strong	Type I Robust and strong	Type I Robust and strong	Type I Robust and strong	Type I Robust and strong	Type I Robust and strong
Molecular weight (kD)	289-440	30-60	165	150	150	265	750
Initial distribution volume (L)	6	3.4	3.5	3.5	3.4	3.5	3.16
Plasma half-life (h)	1	6	20	16	20	60	15
Labile iron release	+++	±	-	-	-	-	-
Direct iron donation to transferrin (% injected dose)	5-6	4-5	1-2	1-2	< 1	1-2	< 1
Test dose required	No	No	Yes	No	No	Yes	No
Iron content (mg/mL)	12.5	20	50	50	100	50	30
Maximal single dose (mg)	125	200-300	20 mg/kg	15 mg/kg (max 1000 mg in one infusion)	20 mg/kg	20 mg/kg	510
Premedication	No	No	No	No	No	TDI only	No
Life-threatening a dverse effects ($x10^6$ doses)	0.9	0.6	3.3	??	??	113	

TDI = total dose infusion

Premedication prior to IV iron administration is often given without any data supporting its benefit. There is even published data that the majority of AEs seen when diphenhydramine is prescribed are due to premedication but often attributed to IV iron.[66]

Antihistamines can cause somnolence, flushing, hypotension and supraventricular tachycardia prompting inappropriate intervention and the conversion of a minor reaction to a serious or life threatening one.[66]

Based on prospective studies of all IV iron formulations with the possible exception of HMW-ID (USA only), where the preponderance of published data suggests caution, and iron isomaltoside (Europe only) for which data is scanty, serious AEs are extremely rare.[3]

Awareness of the clinical nature of AEs and avoidance of unnecessary interventions for minor reactions is paramount.

Premedication prior to IV iron should not be routinely used unless there is a history of allergy to more than one drug, an allergic diathesis or asthma and a history of inflammatory arthritis, wherein both parenteral and oral iron have been shown to exacerbate symptoms. In these cases, we routinely administer 100-200 mg of methylprednisolone prior to the test dose or the total dose calculated for infusion.[67]

Regarding the test dose, in the case of LMW-ID for example, we routinely prepare 1000 mg of this formulation in 250 mL of normal saline and administer 10 to 25 mg of this product infused over 3 to 5 minutes without premedication. If no acute reaction is observed, the remaining solution is infused over the rest of 1 hour.[3,68]

Proper utilization in respect to the recommended doses of each product and the correct infusion time are essential to guarantee the safety.

Conclusions

Oral iron supplements are an inexpensive and effective way of treating IDA patients and their administration, in the absence of inflammation or significant ongoing blood loss, can correct anemia.

Oral iron is a less than ideal treatment because of the high gastrointestinal AE rate, particularly when using ferrous iron compounds; a long treatment course is needed to resolve anemia and to achieve replenishment of the body iron stores.

In cases where oral iron is ineffective, associated with AEs or cannot be used, IV iron compounds are treatment options.

IV iron therapy is clearly better and presents several advantages over oral iron treatment.

Given the proven effectiveness as well as safety profile of IV iron, particularly of IS and ferric carboxymaltose in a broad spectrum of diseases associated with IDA, the current paradigm that oral iron is first-line therapy should be reconsidered.

Based on the preponderance of published evidence, with the exception of high-molecular-weight iron dextran, the differences in safety profile among IV iron products are small when given at the recommended doses and respecting the correct infusion time.

Clinical trials in nephrology, gynecology, gastroenterology, oncology and hematology evaluating more rapid administration of larger doses of iron are needed. So, until reliable comparative data becomes available, one product cannot, and should not, be considered superior in terms of safety profile.

IV iron is safe and probably much safer than most physicians realize. Proper utilization of this important therapeutic modality offers significant clinical benefits by reducing morbidity and mortality from many pathological conditions associated with iron deficiency.

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