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Review on Iron Supplement in Anemia Patients

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ABSTRACT:
Intravenous infusions of iron have evolved from a poorly effective and dangerous intervention to a safe cornerstone in the treatment of iron deficiency. Modern iron formulations are composite nanoparticles composed of carbohydrate ferric oxy-hydroxides. Iron dextran, iron derisomaltose (formerly known as iron isomaltose 1000), ferric carboxymaltose, ferumoxytol, iron sucrose, and sodium ferric gluconate can be infused at different doses and allow correction of the total iron deficit with single or repeated doses in 1–2 weeks depending on the specific formulation. All iron preparations are associated with a risk of severe infusion reactions. In recent prospective clinical trials, the risk of moderate to severe infusion reactions was comparable among all modern preparations affecting <1% of patients.
Hence, intravenous iron therapy is reserved for iron deficiency anemia patients with intolerance or unresponsiveness to oral iron. As per the European drug label, intravenous iron may also be preferred when rapid correction of the iron deficit is required. In patients with inflammation, iron deficiency should also be suspected as anaemiacausedby low transferrin saturation because serum ferritin can be spuriously normal. The main treatment target for i.v. iron is an improvement of the quality of life, for which haemoglobin is a surrogate marker.
Keywords: Anaemia of chronic disease, intravenous iron, iron deficiency anaemia, iron replacement therapy.

INTRODUCTION:

Iron is an essential element and its balance must be maintained for proper physiologic functioning. Blood loss, a major cause of iron deficiency, is highly prevalent (e.g., females with menses and patients with chronic occult gastrointestinal (GI) blood loss) and requires proper diagnosis and management.[1-3] Therapeutic management of IDA is focused primarily on the repletion of iron stores.[4,5] While iron-deficient individuals without inflammation may respond to oral iron therapy, administration of IV iron is beneficial in many patient populations, including those with inflammation (resulting, e.g., from kidney disease, heart failure, or rheumatological diseases), patients who cannot tolerate oral iron, and patients who are non-compliant with oral iron therapy.[6-9] Even under the best of circumstances, oral iron is not well tolerated, and patients are often nonadherent for a variety of reasons, including intolerable side effects and the need for multiple daily doses. Moreover, the frequently poor absorption of oral iron can contribute to suboptimal patient response.[10-12]

Despite beneficial effects in a wide range of patients, administration of IV iron may generate oxidative stress and other inflammatory changes, and the risk-benefit profile of IV iron continues to undergo evaluation in renal dialysis patients, as well as patients with anemia due to other chronic diseases. The long-term effects of IV iron preparations will require further study in relevant clinical settings,as will the long-term deleterious effects of allogeneic blood transfusions.[13-14]

To improve the tolerability of iron formulations, while still allowing substitution of high iron doses, the latest generation of iron preparations was developed, which include ferric carboxymaltose (FCM), ferric derisomaltose (FDI, formerly known as iron isomaltose 1000), and ferumoxytol (FMX) IV iron preparations currently approved in the US are listed in Table 1. Beginning with the first iron dextran product introduced, the recommended cumulative replacement dose for many of these products has been approximately 1000 mg of iron.[15-22]

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Table 1: Current USFDA drug of IV Iron administration

Trade name	Dexferrum (iron dextran injection, USP)	INF (iron dextran injection, USP)	Ferrlecit (sodium ferric gluconate complex in sucrose injection)	Venofer (iron sucrose injection, USP)	Feraheme (ferumoxytol)	Injectafer (ferric carboxymaltose injection)
Manufacturer	American Regent, Inc.	Actavis Pharma, Inc.	Sanofi-Aventis	American Regent, Inc.	AMAG Pharmaceuticals	American Regent, Inc.
Test dose	Yes	Yes	No	No	No	No
Black box warning	Yes	Yes	No	No	Yes	No
FDA-approved indications	Iron deficiency where oral iron administration is unsatisfactory or impossible	Iron deficiency where oral iron administration is unsatisfactory or impossible	Iron deficiency anemia in adult and pediatric CKD patients receiving hemodialysis and receiving ESAs	IDA in adult and pediatric patients with non-dialysis-dependent, hemodialysis dependent, and peritoneal dialysis-dependent CKD	IDA in adult patients with CKD	IDA in adult patients who have an intolerance to oral iron or have had an unsatisfactory response to oral iron or adult patients with non-dialysis-dependent CKD
Total cumulative dose	Dependent on the patient's total iron requirement	Dependent on the patient's total iron requirement	1000 mg	1000 mg	1020 mg	1500 mg

Clinical Application of Iron

The selection of a specific intravenous iron formulation follows the decision if intravenous iron should be started and what the treatment targets are in specific patients. All licensed iron formulations are recommended for patients with iron deficiency as indicated by clinical biochemical analysis and in whom oral iron cannot be used because of ineffectiveness or intolerance. There are minor differences in licensed indications according to the specific drug labels. In Europe, low molecular weight ID and FDI are also recommended in patients in whom a rapid correction of iron deficiency is necessary (e.g. preoperatively). In the USA SFG, IS and FCM is also indicated in patients with chronic kidney disease (e.g., dialysis patients). These minor differences are not reflected in the different recommendations for intravenous iron therapy.[22-24]

Iron Deficiency and Thrombosis

Iron deficiency is known to be associated with reactive thrombocytosis; however, the mechanism behind this phenomenon remains unclear. Studies in adult women show a correlation between platelet count and TfS, as well as serum

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iron,and more severe anemia leads to higher counts.Animal models of iron deficiency recapitulate this observation, which occurs with alterations in megakaryopoiesis and augmented platelet aggregability. Altered platelet function has also been found in patients with iron deficiency and was alleviated by iron therapy.[25-26]

Studies in pediatric as well as adult populations, particularly women, report an association between stroke and iron deficiency anemia.Patients with pulmonary arteriovenous malformations are at higher risk for ischemic strokes, and a low serum level of iron doubles this risk.Anemia is common in both cancer and IBD,and both increase the risk for venous thromboembolism. Thrombocytosis is not uncommon in either conditionand cancer, a high platelet count is an independent risk factor for venous thromboembolism. [27]

Interestingly, iron therapy in IBD has been shown to normalize platelet counts as well as platelet function. Iron therapy also lowers the platelet count in CKD. In cancer, the concurrent administration of intravenous iron and an erythropoiesis-stimulating agent diminishes the incidence of venous thromboembolism more than an erythropoiesis-stimulating agent alone. Collectively, this suggests that proper iron management can potentially diminish the incidence of thromboembolic events by reducing both platelet number and activity.[28-30]

Iron Therapy and Carcinogenesis

Iron homeostasis is tightly regulated to protect against redox damage by free iron yet still provides enough iron for erythropoiesis and cellular function. Fe(II) iron reacts with hydrogen peroxide to form highly reactive hydroxyl radicals (Fenton reaction). Hydroxyl radicals react with all biomolecules, and they can damage nucleotide bases and cause DNA strand breaks. One concern in iron therapy is the potential for tumor promotion or progression.[31]

Several NHANES (National Health and Nutrition Examination Survey) studieshave found that a high TfS (high level of available iron) increases cancer risk in combination with high iron intake. In contrast, the Swedish AMORIS (Apolipoprotein Mortality Risk) study found a positive association between total iron-binding capacity, which increases when the level of available iron is low, and cancer risk. Population studies have found an association between a high level of consumption of red meat and increased colorectal cancer risk, but not when the study population is female. These incongruous results are likely due to a variety of other factors, such as geographic differences in diet, the prevalence of disease, and the prevalence of iron deficiency.[32-33]

Clinical and animal studies of oral iron (primarily ferrous sulfate) and intravenous iron (primarily iron sucrose and iron gluconate) show an increase in oxidative stress markers in different organ systems (reviewed by Koskenkorva-Frank and colleagues). The propensity to induce oxidative stress depends on the amount of free redox-active iron, which in turn depends on drug pharmacokinetics. Intravenous iron compounds vary instability, with less stable complexes such as iron sucrose and iron gluconate dissociating in circulation, and more stable iron complexes such as ferric carboxymaltose and low-molecular-weight iron dextran remaining intact until broken down in the endolysosome.Potential alternative oral iron compounds have been studied, in which the purportedly less reactive Fe(III) iron is combined with a complex to increase bioavailability (Fe[III] hydroxide-polymaltose and ferric maltol).[34-37]

Unfortunately, few studies have directly compared drugs, and the long-term consequences of iron therapy concerning carcinogenesis are as of yet unclear (reviewed by Beguin and colleagues). Nevertheless, the adequate and appropriate administration of iron should diminish the risk of iron oversupply, especially in the context of iron deficiency anemia.[38]

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