IV Iron Products

Summary

The six iron formulations now available in the U.S. are probably of similar safety and efficacy though few head-to head comparisons have been undertaken. The formulations differ in cost per gram of iron and in reimbursement. Physicians should include considerations of cost-effectiveness and convenience when deciding on which formulation to use.

Introduction

For any patient with iron deficiency, intolerant to oral iron or where oral iron is unable or unlikely to work, IV iron is administered. There are six IV iron preparations currently on the US pharmacopoeia. Three relatively new intravenous irons have been approved in the US, ferumoxytol, ferric carboxymaltose and Ferric Derisomaltose, providing an alternative to low molecular weight iron dextran for larger doses of iron to be administered as a single dose or two doses for more rapid iron replenishment. A discussion of each of these preparations follows.

There are six intravenous preparations of iron available all some variation on an iron core and carbohydrate shell.

- **Iron Dextran** – *INFeD* by Sanofi Aventis (low molecular weight) (50 mg elemental iron per ml)
- **Iron Sucrose** - *Venofer* by American Regent (20 mg elemental iron per ml)
- **Sodium Ferric Gluconate** – *Ferrlecit* by Sanofi-Aventis US (12.5 mg elemental iron per ml)
- **Ferumoxytol** – *Feraheme* by AMAG Pharmaceuticals (30mg elemental iron/ml)
- **Ferrric Carboxymaltose** - *Injectafer* by American Regent Inc (50mg elemental iron /mL)
- **Ferric Derisomaltose-** *Monoferric* by Pharmacosmos Therapeutics Inc (100mg elemental iron/mL)

Complete dosing information can be found in the IV Iron Table.

These iron products have different elimination kinetics and different amounts of labile free iron that affect the maximum dose per infusion and rate of infusion.[1]

Iron Dextran

In 1991, low-molecular-weight iron dextran marketed as INFeD was approved for clinical use in the United States. In 1996, high-molecular-weight iron dextran marketed as Dexferrum was approved and provided an alternative to INFeD. These two products replaced Imferon (Fisons, Rochester, NY), which was no longer manufactured, for the treatment of iron deficiency anemia in patients when oral iron administration is unsatisfactory or impossible.[2]

The dextran carbohydrate shell found in some early iron dextran products was associated with rare, severe immunologic responses, sometimes resulting in anaphylaxis and death. Iron dextran carries a black box warning because of this risk of severe, sometimes fatal anaphylactic reactions (loss of consciousness, collapse, difficulty breathing associated with the high molecular weight product.[3,4] High molecular weight iron dextran (Dexferrum) has been removed from the U.S. market.

Current information suggests that low-molecular-weight iron dextran is associated with a markedly lower risk of serious adverse events than high-molecular-weight iron dextran, with a serious adverse event rate of less than 1:250,000.[1,2] The total amount of iron dextran required for the treatment of iron deficiency anemia or iron replacement for blood loss is determined from the patient's body weight, current Hb level, and desired target hemoglobin. The total iron replacement dose of INFeD can be diluted in normal saline and administered as a single IV infusion.

The easiest, least expensive, most efficacious and probably least toxic means of correcting iron deficiency with LMW iron dextran is with a total dose infusion (TDI). The drug is diluted in 250 ml of normal saline. The test dose can be administered as a separate IV push or as a slow infusion of the diluted material. If no adverse events are observed after 10-15 minutes, as is the case in 90% of patients, the remainder of the solution is infused over the balance of one hour. For patients with a history of multiple drug allergies, a prior sensitivity to iron dextran or asthma, 125 mg methylprednisolone should be administered prior to the test dose. Otherwise, premedication should be avoided.[6]

Although anaphylaxis has been reported with LMW ID, Auerbach has administered >70,000 doses in their practice (one dose=100 mg) without a single SAE.[6]

However, two adverse events occur uncommonly, but may be seen. The first of these was described by Fishbane which is the acute onset of chest and back pain or tightness WITHOUT hypotension, tachypnea, tachycardia, wheezing, stridor, or periorbital edema. This harmless reaction, which never leaves residua, abates in minutes and does not recur with rechallenge. Should this reaction occur, NO TREATMENT should be administered, the patient should be reassured, observed for a few minutes, and treatment continued cautiously after abatement of all symptoms. The second adverse event that occurs in approximately 10% of patients consists of arthralgias and myalgias, usually occurring about 24 hours after the infusion. These reactions also never leave residua, abate without therapy, but more quickly when non-steroidal anti-inflammatories are administered.[6]

Iron Sucrose and Ferric Gluconate

Iron sucrose and iron ferric gluconate do not contain the dextran moiety, and the incidence of anaphylactic reactions with these products is thought to be lower. Two well done retrospective studies[7,8] showed that serious acute events with the iron salts were far less likely to occur than with iron dextran and were safe in those previously sensitive to iron dextran. Because of these two papers, iron sucrose and ferric gluconate rapidly replaced iron dextran in dialysis patients. However, the data were confounded by reactions that occurred due to high molecular weight iron dextran. It is now believed that low molecular weight iron dextran has a similar safety profile to iron sucrose and ferric gluconate though head-to-head studies have not been performed.

Unlike iron dextran, where the total dose can be given in a single setting, these agents can only be given in smaller doses not to exceed 200 mg of ferric gluconate and 400 mg for iron sucrose. This requires multiple visits and multiple infusions. However, for dialysis patients coming three times a week for their treatments, the need for frequent IV iron administration is not clinically or logistically relevant.[6]

Iron Sucrose[9]

Iron sucrose has been used in Europe since 1949 and was approved by the FDA in November 2000. It is indicated for the treatment of anemia in dialysis-dependent and non–dialysis-dependent CKD patients. It is approved in both adult and pediatric patients. Both iron sucrose and ferric gluconate have been used successfully in patients who are intolerant to iron dextran. Iron sucrose has also been used successfully in patients intolerant to both iron dextran and ferric gluconate.

Ferric Gluconate[10]

Ferric gluconate was first used in Europe in 1977, was approved by the FDA for use in the United States in February 1999. It is currently indicated for the treatment of iron deficiency anemia in adult and pediatric patients undergoing chronic hemodialysis who are receiving supplemental ESA therapy. Both iron sucrose and ferric gluconate have been used successfully in patients who are intolerant to iron dextran. There are no data available on the use of ferric gluconate in patients intolerant to iron sucrose, or both iron dextran and iron sucrose.[9]

Ferumoxytol[11]

In June of 2009, ferumoxytol, was approved for administration to iron deficient patients with chronic renal failure. In February 2018, Ferumoxytol received approval to broaden its label to include all eligible adult iron deficiency patients who have

intolerance to oral iron or have had an unsatisfactory response to oral iron.

This drug is supplied in a 510 mg vial, increasing convenience by decreasing pharmacists' time for preparation. There is no data at the present time with the administration of higher doses. Therefore, complete replacement for iron deficient patients requires at least two visits, at least 3 days apart. Ferumoxytol may be given as a 510 mg IV Infusion in 50-200 mL 0.9% sodium chloride or 5% dextrose over at least 15 minutes.

Adverse events are uncommon. Anaphylaxis has been reported with this drug as well as with all of the other iron compounds. In clinical studies, serious hypersensitivity reactions were reported in 0.2% (3/1726) of subjects receiving ferumoxytol. Originally approved for administration over 20-30 seconds, serious reactions are likely less common with the longer infusion time and similar to the serious adverse event rate with the other iron preparations. Other adverse reactions potentially associated with hypersensitivity (e.g., pruritus, rash, urticaria, or wheezing) were reported in 3.7% (63/1726) of these subjects.

Ferric Carboxymaltose[12]
In 2013, ferric carboxymaltose became available in the US. It has been used in Europe and other countries since 2009. Ferric carboxymaltose is indicated for the treatment of iron deficiency anemia (IDA) in adults who either cannot tolerate or have not responded well to oral iron. Ferric carboxymaltose can be administered as a single dose of up to 750 mg and undiluted as an intravenous push injection at a rate of 100 mg/minute or as an intravenous infusion in up to 250 mL 0.9% sodium chloride injection over the course of at least 15 minutes. Therefore, complete replacement for iron deficient can be achieved in only one to two visits, separated by at least 7 days for a cumulative dose of 1,500 mg.

In clinical trials, serious anaphylactic/ anaphylactoid reactions were reported in 0.1% (2/1775) of subjects receiving Injectafer. Other serious or severe adverse reactions potentially associated with hypersensitivity which included, but not limited to, pruritus, rash, urticaria, wheezing, or hypotension were reported in 1.5% (26/1775) of these subjects.

Ferric Derisomaltose[13]
In 2020, ferric derisomaltose became available in the US. It has been used in Europe and other countries since 2009 under the drug name, iron isomaltoside. Ferric derisomaltose is indicated for the treatment of iron-deficiency anemia (IDA) in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron; who have non-hemodialysis dependent chronic kidney disease. Ferric derisomaltose can be administered as a single 1,000 mg dose for patients weighing 50 kg or more. For patients weighing less than 50 kg ferric derisomaltose is administered as 20 mg/kg actual body weight as an intravenous infusion. Ferric derisomaltose is diluted in 100 mL to 500 mL of 0.9% Sodium Chloride Injection, USP. The final diluted concentration should be more than 1 mg iron/mL. and administer the prepared solution via intravenous infusion over at least 20 minutes. Ferric derisomaltose treatment can be repeated if iron deficiency anemia reoccurs.

In clinical trials in patients with IDA and CKD, serious or severe hypersensitivity were reported in 0.3% (6/2008) of the Monoferric treated subjects. These included 3 events of hypersensitivity in 3 patients; 2 events of infusion-related reactions in 2 patients and 1 event of asthma in one patient.

References

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