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REVIEW ARTICLE

Intravenous Iron Sucrose

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ABSTRACT

Iron deficiency is a major worldwide health problem. There is recent evidence that anemia is the last manifestation of the syndrome. Advances in outlining the physiology of iron deficiency have been made; gaps remain in the current understanding. While oral iron supplement remains the mainstay, some indications for intravenous (IV) administration have developed. In this review, we will highlight the indications and prerequisites of IV iron therapy, dosage, safety, and method of administration.

Keywords: Dose calculation, Intravenous iron preparations, Iron sucrose, Intravenous iron therapy.

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INTRODUCTION

Intravenous (IV) iron sucrose has a very high potential for reducing the burden of iron deficiency anemia (IDA) because it overcomes the problems of compliance and absorption, compared with oral iron supplementation and has an excellent safety record. Through a single total dose infusion of iron sucrose, it is possible to handle the commonest medical disorder of pregnancy, thereby dramatically reducing maternal morbidity and mortality, while improving the quality of life of women in the developing world.

INDICATIONS FOR INTRAVENOUS IRON SUCROSE THERAPY

- Intolerance to oral iron
- Poor compliance to oral iron
- Inadequate absorption due to gastrointestinal disorders – malabsorption, achlorhydria
- Lack of response to oral iron
- Pregnant women with severe IDA, presenting late in pregnancy
- As the first-line therapy in cases of moderate and severe IDA in second and third trimester of pregnancy
- Postpartum anemia.

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INTRAVENOUS IRON SUCROSE

Chemistry

Iron sucrose injection, USP is a sterile, aqueous, complex of polynuclear iron (III)-hydroxide in sucrose for IV use. Its molecular weight (MW) is approximately <60,000 Da.

Availability

Intravenous iron sucrose is available as 2.5 and 5 mL single-dose ampoules. One ampoule of 2.5 mL contains 50 mg and one ampoule of 5 mL contains 100 mg of elemental iron.

Safety Profile

- Rarely, minor adverse effects[1]
- Lower dose of Iron sucrose (100 mg Fe/kg) produces less or almost no adverse effects
- Allergic reactions: 3.3 cases/million/year.

Method of Administration

Monitor carefully patients for signs and symptoms of hypersensitivity reactions during and following each administration of Iron Sucrose. Iron Sucrose must only be administered by the IV route. This may be by a slow IV injection or by an IV drip infusion.

Posology

The cumulative dose of iron sucrose must be calculated for each patient individually and must not be exceeded.

Calculation of Dosage

The total cumulative dose of iron sucrose, equivalent to the total iron deficit (mg), is determined by the hemoglobin (Hb) level and body weight (BW). The dose of iron sucrose must be individually calculated for each

patient according to the total iron deficit calculated with the following Ganzoni formula, for example:

$$\text{Total iron deficit [mg]} = \text{BW [kg]} \times (\text{target Hb} - \text{actual Hb}) \text{ [gm/dL]} \times 2.4^{*} + \text{storage iron [mg]}$$

- Below 35 kg BW: Target Hb = 13 gm/dL and storage iron = 15 mg/kg BW
- 35 kg BW and above: Target Hb = 15 gm/dL and storage iron = 500 mg

$$\text{Total iron sucrose to be administered (in mL)} = \frac{\text{Total iron deficit [mg]}}{\text{20 mg iron / mL}}$$

Total amount of iron sucrose (mL) to be administered according to BW, actual Hb level, and target Hb level.*

Intravenous Drip Infusion

Intravenous iron sucrose is administered by IV Infusion:

- The infusion is administered as every 2.5 mL iron sucrose in 100 mL of 0.9 % NaCl at the rate of 100 mL/30 minutes.
- Unused diluted solution must be discarded.
- Maximum dose: A maximum of 200 mg of elemental iron in 100 mL NS over 30 minutes, on alternate days given.
- A total dose of 1.0 gm can be given in 4 to 10 sittings.

Dilution must take place immediately prior to infusion and the solution should be administered as follows:

Iron sucrose dose (mg of iron)	*Iron sucrose dose (mL of iron)*	*Maximum dilution volume of sterile 0.9% m/V NaCl solution*	*Minimum infusion time*
50 mg	2.5 mL	50 mL	8 min
100 mg	5 mL	100 mL	15 min
200 mg	10 mL	200 mL	30 min

For stability reasons, dilutions to lower iron sucrose concentrations are not permissible.

Intravenous Injection

Iron sucrose may be administered by slow IV injection at a rate of 1 mL undiluted solution per minute and not exceeding 10 mL iron sucrose (200 mg iron) per injection.

Refractory Cases

If Hb levels do not improve after 3 to 4 weeks of therapy, the cause of anemia should be reevaluated. For a non-IDA, the cause should be treated and blood transfusion should be considered. Also, for a refractory IDA, blood transfusion should be considered.

Prerequisites for Intravenous Iron Sucrose Therapy

- It should be given under proper supervision. At least a doctor should be available while giving it. This is required to handle anaphylactic shock.[2]
- Close monitoring is required to observe the rate of infusion and patient vitals, especially the pulse rate and blood pressure.
- An emergency tray containing injection Adrenaline, injection. Hydrocortisone, and oxygen should be available for management of anaphylactic reactions.
- Cardiopulmonary resuscitation facility should be available, in case a patient collapses because of anaphylactic shock.

Contraindications to Iron Sucrose

General contraindications are iron overload, non-IDA, and known hypersensitivity to iron sucrose.

Side Effects of Iron Sucrose

There can be hypotension, headache, vomiting, nausea, dizziness, joint ache, paresthesia, abdominal and muscle pain, edema, and cardiovascular collapse side effects, which are rare in dose of 100 mg/day. They appear if it is infused in higher dose or the rate of infusion is very slow and very fast (the norm of 100 mL/30 minutes should be followed).

Studies

Several authors have now reported on their experience with use of parenteral iron therapy for IDA in pregnancy, with faster increases in Hb and better replenishment of iron stores in comparison with oral therapy, particularly demonstrated for iron sucrose[3,4] and iron (III) carboxymaltose.[5,6]

A large retrospective study reported fewer postpartum transfusions in the group treated with IV iron.[7]

There is a paucity of good quality trials that assess clinical outcomes and safety of these preparations.[8]

Iron sucrose has a higher availability for erythropoiesis than iron dextran and experience suggests a good safety profile in pregnancy.[9] Its use is limited by the total dose that can be administered in one infusion, requiring multiple infusions. The newer preparations, iron III carboxymaltose and iron III isomaltoside, aim to overcome this problem, with single-dose administration in an hour or less (Table 1).[10-12]

*Factor 2.4 = 0.0034 (iron content of Hb = 0.34%) × 0.07 (blood volume = 7% of BW) × 1000 (conversion of [gm] to [mg]) × 10

Table 1: Pharmacologic characteristics of the main intravenous iron complexes

	Sodium ferric gluconate complex[a]	*Iron sucrose*[b]	*High MW iron dextran*[c]	*Low MW iron dextran*[d]	*Ferric carboxymaltose*[e]	*Ferumoxytol*[f]	*Isomaltoside 1,000*[g]
Trade name	Ferlicit®	Venofer®	Dexferrum®	Cosmofer® INFeD®	Ferinject®	FeraHeme®	Monofer®
Carbohydrate shell	Gluconate	Sucrose	Dextran (branched polysaccharide)	Dextran (branched polysaccharide)	Carboxymaltose (branched polysaccharide)	Polyglucose sorbitol carboxymethylether	Isomaltoside 1,000 (linear oligosaccharide)
MW (Da)[#]	37,500	34,000–60,000	265,000	165,000	150,000	750,000	150,000
Classification[h]	Type III	Type II	Type I	Type I	Type I	Type I	Type I
Iron content (mg/mL)	12.5	20	50	50	50	30	100
Half-life (hours)	1	6	9–87	5–20	7–12	15	20
Maximum single dose (mg)	125	200	20 mg/kg	20 mg/kg	15 mg/kg (max 1,000 mg)[*]	510	20 mg/kg
Reactivity with transferrin	High	Medium	Low	Low	Low	Low	Low
Test dose required[##]	No	No	Yes	Yes	No	No	No

Notes: [a]Ferlecit® prescribing information. Sanofi Aventis, Inc Bridgewater, NJ, USA. [b]Venofer® prescribing information. Vfor Pharma Ltd Glattbrugg, Switzerland. [c]Dexferrum® INFeD® prescribing information, Watson Pharma, Inc, Morristown, NJ, USA. [d]Cosmofer® prescribing information, Pharmacosmos A/S, Holbæk, Denmark. [e]Ferinject® Injectafer® prescribing information. Vifor Pharma Ltd Glattbrugg, Switzerland. [f]FeraHeme® prescribing information. AMAG Pharmaceuticals, Inc Waltham, MA, USA. [g]Monofer® prescribing information. Pharmacosmos A/S, Holbæk, Denmark. [h]Type I complexes are robust and strong and thus release only minimal amounts of ionic iron in the blood stream. Type II complexes are semi-robust and moderately strong and consequently less stable than Type I complexes. Type III complexes are the least stable and therefore release relatively large amounts of ionic iron into the blood stream. Type IV complexes are mixed complexes. They are heterogeneous mixtures, which may induce side effects such as allergic responses and saturation of the iron transport system. [#]The molecular weight in this table are those given by the manufacturer, but since they are measured with different standards the values are not totally comparable. [##]This is only the case in USA. In Europe, the test dose has been removed for all IV iron products. *In Europe, for infusion the maximal iron dose is 20 mg/mL[12]

CONCLUSION

Despite the high incidence of anemia associated with iron deficiency, there is paucity of good quality trials assessing clinical maternal and neonatal effects of iron administration in women with anemia. Daily oral iron treatment improves hematological indices but causes frequent gastrointestinal adverse effects. Parenteral (IV) iron enhances hematological response, compared with oral iron, but there are concerns about possible important adverse effects.

Large, good quality trials assessing clinical outcomes are required.

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