The use of Parenteral Iron in Pregnancy

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Content

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- Pharmacological properties
- Efficacy profile
- Safety profile
- Cost effectiveness
- Dosage & administration

- Disclosure: Sponsored by Menarini
Indications for parenteral iron therapy

- Failure to oral iron therapy
- Non compliance/intolerance to oral iron
- 1st time seen during last 8-10 weeks with severe anemia
- Malabsorption / IBS/chronic bowel disease
- Small bowel resection
- When hemorrhage is likely to continue
- Contraindication to blood transfusion
- Contraindication to oral therapy
- Patients refuse blood transfusion
History of IV Iron Therapy

1932: Fe(OH)_3
1947: Iron Saccharide (HMWID)
1947: Imferon (HMWID)
1954: 1st Prospective Study IV Iron in US
1964: INFeD (LMWID in US)
1991: DexFerrum (HMWID)
1996: Ferrlecit (FG)
1999: Venofer (IS)
2000: CosmoFer (LMWID)
2001: Ferinject (Iron carboxy-Maltose)
2007: Monofer (Iron isomaltoside 1000)
2009: Feraheme (Ferumoxytol)
2010: Rienso (Ferumoxytol)
2012: Monofer (Europe)
2010: CosmoFer (Europe)
2007: INFeD (Europe)

Parenteral Preparations

Intravenous preparation
   a) Iron dextran (Imferon), (Cosmofer) etc.
   b) Iron sucrose (venofer)
   c) Sodium ferric gluconate (ferrlecit)

Intramuscular preparation
   a) Iron Sorbitol Citrate in dextrin (Jectofer)
   b) Iron Dextran (Imferon), (Cosmofer)

Iron dextran: 50 mg/mL, Iron sucrose: 20 mg/mL
Ferric gluconate: 12.5 mg/mL
Recently, in Tennessee, a physician ordered LMW iron dextran (INFeD, Watson, Morristown, NJ) in a patient for iron deficiency anemia when oral iron had been ineffective and tolerated poorly. The pharmacist substituted the less expensive HMW iron dextran (Dexferrum, American Regent, Shirley, NY). Anaphylaxis shortly after receiving a test dose of HMW iron dextran was followed by death.

We urgently recommend avoiding use of HMW iron dextran in all clinical practice settings. We also recommend that the FDA withdraw this formulation of intravenous iron.
Physiochemical properties Iron Dextran

- Iron Dextran solution for injection contains iron in a stable aqueous iron(III)-hydroxide dextran complex, which is analogous to the physiological ferritin.

- The pH is adjusted to approximately 5.2 – 6.5 (neutral) by the use of sodium hydroxide or hydrochloric acid. - less risk of tissue damage, hence can be used for I.M

- The formulation is characterized by a strong colloidal complex of a ferric core shielded by tightly bound dextran chains.

- No preservatives are added.
The product

- Pharmacological properties
- Efficacy profile
- Safety profile
- Cost effectiveness
- Dosage & administration
Efficacy and Safety of Total Dose Infusion of Low Molecular Weight Iron Dextran in the Treatment of Iron Deficiency Anemia During Pregnancy

Rukhsana Ayub¹, Nabia Tariq¹, Malik Muhammad Adil², Moeen Iqbal², Ayesha Junaid³ and Tara Jaferry²

- 100 pregnant woman, 50 controls

- “The WHO technical working group on the prevention and the treatment of severe anemia has documented that parenteral iron therapy produces a rapid and complete correction of iron deficiency, including replacement of iron stores producing a more rapid erythropoietic response than oral iron replacement.”

- “We conclude that the total parenteral iron replacement with low molecular weight iron dextran is an effective and safe method for the treatment of iron deficiency anemia in a selected group of pregnant women.”

Clinical use in different indications
EFFICACY OF TDI

• “According to World Health Organization (WHO), oral iron programs have often failed to reduce frequency of iron-deficiency anemia. High levels of iron-deficiency anemia exist in pregnancy despite routine use of iron prophylaxis adopted by many centres in the developing world.”

• “The study illustrates that total dose infusion of low molecular weight iron dextran increases hemoglobin faster than oral iron (ferrous sulphate) in the treatment of iron deficiency anemia during pregnancy. It is also quite safe as mild side effects of palpitations and flushing was observed in only 4% of patients.”

• “A major advantage of total dose iron, given as a single dose, is the relative ease and confirmed patient compliance and does not require repeated visits to clinic.”
The product

- Pharmacological properties
- Efficacy profile
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Safety profile

**CosmoFer®**: The short term safety; study on 6,690,000 doses of low Mw Iron dextran

The ADEs reported in 6,690,000 doses (equivalent to 100 mg IV iron) of CosmoFer® were:
- 0.0003% Life Threatening ADEs
- 0.004% total ADEs

The relative safety of parenteral iron formulations using data from the US Food and Drug Administration on reported adverse drug events relating to the provision of intravenous iron during 1998-2000.
All iv iron preparations carry a small risk of causing adverse reactions which can be life-threatening if not treated promptly.

The benefits of iv iron outweigh their risks in the treatment of iron deficiency when the oral route is insufficient or poorly tolerated.
Iv iron products should be administered only when staff trained to evaluate and manage anaphylactic reactions, as well as resuscitation facilities, are immediately available.

A test dose is not appropriate as it may give false reassurance, no test dose should be applied.

Patients should be closely monitored for signs of hypersensitivity during and at least 30 minutes after each administration.
European Medicines Agency (EMA) has recently concluded¹:

A. All IV-iron compounds have a positive risk/benefit ratio

B. Currently available data cannot be used to conclude any differences in safety profile between available products.

For IV-iron compounds in general on the European market, most adverse events² are mild and does not require any actions, moderate events may require a temporary reduction in infusion speed, a temporary halt or a complete stop. Severe adverse events must be treated by a complete stop with IV-iron and appropriate medical treatment according to the severity of symptoms

Author conclusion:
Our data suggest that AE rates with IV iron are acceptable. More widespread use of LMWD, in particular, which can be given safely as a total dose infusion (TDI), should be considered.
NON- SERIOUS ADRs:

- **Acute myalgias (chest and back tightness)** occur relatively frequent (1%) and are not serious. Symptoms as: itching, mild dyspnoea and wheezing, chest pain, nausea and headache are examples of mild reactions that occur transiently in the beginning of the infusion and abates after a short period of time without treatment.

- These reaction abates within minutes without treatment and does not recur with re-challenge.

- The above should be managed by:\(^2\):
  1. walking away
  2. taking your OWN pulse
  3. returning in five minutes and re-challenging

1. Auerbach, Lancet, 2007
2. Oral communicated by Auerbach
The acute myalgias was also described by Fishbane (AJKD1996) as a syndrome:

• “The Fishbane reaction” occurs in 1 in 200 patients receiving LMW-ID, and consists of arthralgia, myalgia of the chest and flank.

• Usually occurs with or after the test dose

• WITHOUT associated hypotension, tachypnea, tachycardia, wheezing, stridor and periorbital edema

• Reaction routinely abates without treatment and rarely occurs with re-challenge


Safety profile
### Key features of type-1 reactions and Complement activation related pseudo allergy (CARPA)

<table>
<thead>
<tr>
<th>Type-1 IgE mediated</th>
<th>CARPA (Complement mediated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction arises after repeated exposure to allergen</td>
<td>Reaction arises at first treatment (no prior exposure to allergen)</td>
</tr>
<tr>
<td>Reaction is <strong>stronger</strong> after repeated exposures</td>
<td>Reaction is <strong>milder</strong> or absent after repeated exposures</td>
</tr>
<tr>
<td>Reaction does not cease without treatment</td>
<td><strong>Spontaneous resolution when infusion is paused</strong></td>
</tr>
</tbody>
</table>

A GUIDE TO IV IRON ADMINISTRATION:
HYPERSENSITIVITY REACTIONS TO INTRAVENOUS IRONS: GUIDANCE FOR RISK MINIMIZATION AND MANAGEMENT

Rampton et al., Haematologica, 2014, 99:1671-1676
Guide to management of HSR

### Symptoms
- Itching, flushing, urticaria, chest tightness, cough, shortness of breath, tachycardia, hypertension or hypotension, nausea and/or back/joint pain

### Management

#### The patient is having a mild to moderate hypersensitivity reaction
- Stop iron infusion
- Alert attending physician
- Monitor pulse, BP, respiratory rate and oxygen saturation
- Consider iv hydrocortisone 100-200mg
- Rapidly infuse 500 mL 0.9% NaCl in case of hypotension or tachycardia

**Patient better?**

#### Yes
- Restart iron infusion at 50% of, and slowly increase to initial rate if tolerated
- Observe for at least an hour
- Discuss with attending physician
- Document the event
- Consider future treatment strategy

**NO**

#### The patient is having a severe hypersensitivity reaction
- Stop iron infusion
- Call fast response team
- Initiate local anaphylaxis protocol (eg adrenaline im (0.5mg 1/1000) or iv (0.1mg 1/10000), nebulised B2 agonist, further volume load, iv hydrocortisone, O2 face mask, ACLS (if necessary))

**Patient better?**

#### Yes
- Do NOT restart iron infusion
- Observe for at least an hour
- Discuss with attending physician
- Document the event
- Consider future treatment strategy

**NO**

#### Transfer quickly to intensive care

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Developed by Professor DS Rampton based on 'Hypersensitivity reactions to intravenous iron: guidance for risk minimisation and management' Haematologica 2014;99:1671-6
Ideally the long term safety of parenteral iron formulations should be assessed through large scale clinical trials that run for a sufficient number of years.

Unfortunately such trials are currently not available for any parenteral iron formulation.

The long term consequences of the toxicological profiles therefore have to be extrapolated from in-vitro and in-vivo animal studies combined with the measurement of surrogate endpoints in humans.
Pai et al. (2007) published a Comparison of Oxidative Stress Markers After Intravenous Administration of Iron Dextran, Sodium Ferric Gluconate, and Iron Sucrose in Patients Undergoing Hemodialysis

- First study to compare INFeD®/CosmoFer®, Ferrlecit ® and Venofer®
- 12 Hemodialysis patients
- Significant more non-transferrin-bound iron after administration of Sodium Ferric Gluconate and Iron Sucrose compared to Iron dextran
Long term safety profile – Comparison of oxidative stress markers

SFG: sodium ferric gluconate, IS: iron sucrose, ID: iron dextran
AUC: area under the concentration-time curve
* Differences were significant for SFG and IS vs ID (p<0.005); no significant differences were found between SFG and IS

Quote:

Iron dextran, a very stable iron-carbohydrate complex, was associated with minimal non-transferrin-bound iron appearance compared with sodium ferric gluconate and iron sucrose. The two latter products also produced more lipid peroxidation than iron dextran.
Stefansson B et al. (2011): Oxidative stress after injection of iron sucrose (IS) and iron dextran (ID) was compared.

- 20 hemodialysis patients, Plasma iron and oxidative stress parameters were measured before and 10 min after IV injection of 100mg IS an ID.

- Conclusion: Free iron was higher after iron sucrose compared to iron dextran. Oxidative stress marker was increased after iron sucrose but not iron dextran.
Iron dextran is more stable than iron sucrose which in turn is more stable than ferric gluconate. The stability of the iron complexes is clinically relevant because stable complexes are less likely to lead to toxicity. This is reflected in the maximal single dosage recommendations: CosmoFer 20 mg/kg body weight;...
Cost effectiveness
Peebles et al. (2004) conducted an interim audit to examine the clinical outcomes and financial impact of a change to service provision from intravenous iron sucrose (Venofer®) to intravenous low Mw iron dextran (CosmoFer®) administered as total dose infusions (TDI).

The mean dose of iron administered was 1,200 mg (range 900-1,500 mg).

"This cost impact study reveals that by adopting a policy of administering low-molecular-weight iron dextran complex as a TDI, substantial cost savings can be made while improving clinical outcomes."

Cost-effectiveness

**CosmoFer**® can be administered up to 20mg/kg as TDI (Total Dose Infusion)

<table>
<thead>
<tr>
<th>Cost Driver</th>
<th>CosmoFer®</th>
<th>Iron Sucrose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travel costs</td>
<td>One hospital visit</td>
<td>Four hospital visits</td>
</tr>
<tr>
<td>Giving set</td>
<td>One</td>
<td>Four</td>
</tr>
<tr>
<td>Cannula</td>
<td>One</td>
<td>Four</td>
</tr>
<tr>
<td>Dressing</td>
<td>One</td>
<td>Four</td>
</tr>
</tbody>
</table>

Total Dose Infusion improves compliance, reduces number of injections and hospital visits

**CosmoFer**® IV, IM and TDI
• Pharmacological properties
• Efficacy profile
• Safety profile
• Cost effectiveness
• Dosage & administration
**Dosage and Administration**

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**Dose Calculation from Ganzoni formula**

Based on Target Hb in Malaysian CPG on the Management of Anemia in Pregnancy and Chronic Kidney Disease

Body weight (kg) x (target Hb - actual Hb) (g/dL) x 2.4 + mg iron for iron stores

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
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<tr>
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<tr>
<td>50</td>
<td>11</td>
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<td>9</td>
<td>7</td>
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<td>60</td>
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<td>65</td>
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<td>70</td>
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<td>11</td>
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<tr>
<td>90</td>
<td>16</td>
<td>14</td>
<td>11</td>
<td>9</td>
<td>7</td>
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<td></td>
</tr>
</tbody>
</table>

No. of Ampoules (2ml)

Note: Based on target Hb = 11g/dL, body weight ≥ 35kg, and depot iron = 500mg
CosmoFer® solution for injection can be administered by an intravenous drip infusion or by a slow intravenous injection of which the intravenous drip infusion is the preferred route of administration, as this may help to reduce the risk of hypotensive episodes.

### Intravenous drip infusion

<table>
<thead>
<tr>
<th>Dose</th>
<th>100-200mg (2-4ml) iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>1. Infuse the first 25 mg iron slowly over 15 minutes.</td>
</tr>
<tr>
<td></td>
<td>2. If no adverse reactions occur within 15 minutes, administer the rest infusion at a rate not exceeding 100ml / 30min.</td>
</tr>
</tbody>
</table>

### Intravenous injection

<table>
<thead>
<tr>
<th>Dose</th>
<th>100-200 mg (2-4ml) iron (0.2 ml / min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>1. Inject 25 mg iron slowly over a period of 1-2 minutes.</td>
</tr>
<tr>
<td></td>
<td>2. If no adverse reactions occur within 15 minutes, administer the rest injection.</td>
</tr>
</tbody>
</table>
Intramuscular injection (used by Klinik Kesihatan):

- Attributed by the pH neutral solution, can be administered as a series of undiluted intramuscular injections up to 100mg iron.

- Iron Dextran must be given by deep intramuscular injection to minimise the risk of subcutaneous staining. It should be injected only into the upper outer quadrant of the buttock. A 20 - 21 gauge needle at least 50 mm long should be used for normal adults. For obese patients the length should be 80 - 100 mm whereas for small adults a shorter and smaller needle (23 gauge x 32 mm) is used.

Deep I/M Z- technique Inject air / saline before withdrawing
Other Intramuscular injection therapy

The compounds used in intramuscular therapy are:
1. Iron-dextran (Imferon)
2. Iron- sorbitol-citric acid complex in dextrin(Jectofer)
( Both contain 50mg of elemental iron in one milliliter)
   Total dose is calculated as in i/v therapy .

- Dose of iron sorbitol complex is to be adjusted because of its 30% excretion in urine.
- Oral iron should be suspended at least 24 hours prior to I /M therapy to avoid reaction.
Iron dextran therapy
Total Dose Infusion

- Must be given in premises with emergency facilities
- All TDI must have a test dose, even though is may not be full prove & watch for 30 mins
- Must watch for ADR during & after (delayed) after TDI
- Keep resus trolley standby, hydrocortisone standby
• Due to the tightly bound iron complex, CosmoFer® can be administered as Total dose infusion (TDI) with up to 20 mg/kg administered over 4-6 hours in one single infusion.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Up to 20 mg/kg bodyweight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration (Intravenous infusion over 4-6 hours)</td>
<td></td>
</tr>
<tr>
<td>1. Infuse the first 25 mg iron slowly over 15 minutes.</td>
<td></td>
</tr>
<tr>
<td>2. If no adverse reactions occur within 15 minutes, administer the rest infusion (infusion rate may be increased progressively 45 to 60 drops / minute).</td>
<td></td>
</tr>
</tbody>
</table>
Stability in a larger volume

- CosmoFer is nanoparticles – like all other iv iron products and we know that nanoparticles get unstable when they are diluted too much.
- This have been the rationale behind the chosen degree of dilution with both CosmoFer in the development of the products (max. 500 ml)
- We don’t recommend to dilute the product too much (500 ml) and risk the stability – if you like the patient to have more fluid you can simply just give another bag of saline or alike afterwards.
Advantages of Intravenous route

- It eliminates repeated and painful intramuscular injections.
- The treatment is completed in a day and the patient may be discharged much earlier from the hospital.
- It is less costly compared to the repeated intramuscular therapy.
- Superior to restore Hb & iron storage than IM

Limitations of Intravenous route:

- As the maximum haemoglobin response does not appear before four to nine weeks, the method is unsuitable if at least four weeks time is not available, to raise the haemoglobin to a safe level of 10 gm% before delivery.
- Previous history of reaction to parental therapy is a contraindication for its use.
Case of severe anaemia refuse blood transfusion
Iron dextran therapy

• Adverse reaction
  – Nausea, vomiting
  – Pruritus
  – Bronchospasm
  – Hypotension
  – Arthralgia, Arthritis

• Contraindication
  – Thalassaemia, iron overload or disturbances in utilisation of iron (e.g. haemochromatosis, haemosiderosis).
  – Known allergy to iron dextran
  – Non-iron deficiency anaemia (e.g. haemolytic anaemia).
  – Decompensated liver cirrhosis and hepatitis.
  – Acute or chronic infection, because parenteral iron administration may exacerbate
    – bacterial or viral infections.
  – Acute renal failure.
<table>
<thead>
<tr>
<th></th>
<th>Cosmofer (Low Mw iron dextran)</th>
<th>Iron Sucrose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of ampoule</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Ml per ampoule/vial</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Mg iron per ml</td>
<td>50 mg/ml</td>
<td>20 mg/ml</td>
</tr>
<tr>
<td>I.V</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>I.M</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Total Dose Infusion</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Maximum Dosage Rate of administration</td>
<td><strong>IV injection: 200mg</strong></td>
<td><strong>IV injection: 200mg</strong></td>
</tr>
<tr>
<td></td>
<td>0.2ml/min (20 mins)</td>
<td>1 ml/ min (10 mins) maximally 3 times/week</td>
</tr>
<tr>
<td></td>
<td><strong>IV drip infusion: 200mg</strong></td>
<td><strong>Drip infusion: 7mg/kg</strong></td>
</tr>
<tr>
<td></td>
<td>100ml/30 min (30 mins)</td>
<td>up to 500mg/week</td>
</tr>
<tr>
<td>TDI</td>
<td><strong>TDI: 20mg/kg body weight by TDI</strong></td>
<td>3.5 hrs</td>
</tr>
<tr>
<td></td>
<td>4-6 hrs</td>
<td>*Assuming a patient weighing 50kg, 1000mg/ infusion</td>
</tr>
<tr>
<td></td>
<td>*Assuming a patient weighing 50kg, 350mg/ infusion</td>
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</tbody>
</table>
CosmoFer® iron therapy
low MW iron dextran

• EFFECTIVE AND FLEXIBLE....
  
  – CosmoFer® is the only globally available parenteral iron formulation that can be administered both IV, IM and up to 20mg/kg as total dose infusion (TDI)\textsuperscript{12,29,32}
  
  – CosmoFer® administered as TDI, improves compliance and reduces the number of injections and hospital visits\textsuperscript{51}
  
  – CosmoFer® has been proven to be effective in patients who cannot tolerate oral iron.

• WITH A WELL DOCUMENTED SAFETY PROFILE.
  
  – CosmoFer® is a stable, tightly bound low Mw Iron dextran complex with established short and long-term safety profile\textsuperscript{13,14,15,16,68}
  
  – CosmoFer® offers a well documented clinical experience from > 70 million doses and is today used in more than 50 countries\textsuperscript{4}

2. Iron deficiency and iron–deficiency anemia in women’s health, Laura Percy, Diana Mansour, TOG obstetrician & Gynaecologist volume 19, 2017

THANK YOU