Adverse Events with IV iron

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Disclosures

- I have no financial disclosures
Disclosures

• This presentation contains published studies of unapproved methods of administration
IN GOD WE TRUST, ALL
History of IV Iron

- Fe(OH)₃
- Iron Saccharide
- Imferon (HMWID)
- 1st US Report (1st Prospective Study IV Iron in US)
- 1980 INFeD (LMWID)
- 1991 DexFerrum (HMWID)
- 1994 Ferrlecit (FG)
- 1999 Venofer (IS)
- 1999 Feraheme (ferumoxytol)
- Ferric carboxymaltose Iron isomaltoside

- 1932
- 1947
- 1954
- 1964
- 1980
- 1991
- 1996
- 1999
- 2000
- 2009
- 2011
<table>
<thead>
<tr>
<th>Agent</th>
<th>FDA-approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferric gluconate&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Adult and pediatric HD patients aged 6 years and older receiving ESAs</td>
</tr>
<tr>
<td>Iron sucrose&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Dialysis-dependent patients with CKD receiving ESAs</td>
</tr>
<tr>
<td></td>
<td>Nondialysis-dependent patients with CKD receiving or not receiving ESAs</td>
</tr>
<tr>
<td>Iron dextran&lt;sup&gt;3-4&lt;/sup&gt;</td>
<td>Patients with documented iron deficiency in whom oral iron administration is unsatisfactory or impossible</td>
</tr>
<tr>
<td>Ferumoxytol&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with CKD</td>
</tr>
<tr>
<td>Ferric carboxymaltose&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Patients with documented iron deficiency in whom oral iron administration is unsatisfactory or impossible</td>
</tr>
<tr>
<td></td>
<td>Iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with CKD</td>
</tr>
</tbody>
</table>


## IV Iron Dosing

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Approved Dosing</th>
<th>Maximum Safe Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferric gluconate</td>
<td>125mg over 10-60 min</td>
<td>250mg over 1 hour¹</td>
</tr>
<tr>
<td>Iron sucrose</td>
<td>100-400mg over 2-90 min</td>
<td>300mg over 2 hour²</td>
</tr>
<tr>
<td>Iron dextrans</td>
<td>100mg over 2 min</td>
<td>TDI over 1-4 hours³-⁴</td>
</tr>
<tr>
<td>Ferumoxytol</td>
<td>510mg in &lt; 17 seconds</td>
<td>1020mg over 15 minutes⁵</td>
</tr>
<tr>
<td>Ferric carboxymaltose</td>
<td>750mg over 15 min</td>
<td>1000mg over 15 min⁶</td>
</tr>
<tr>
<td>Iron isomaltoside</td>
<td>20mg/kg over 15 min</td>
<td>20mg/kg over 15 min⁷</td>
</tr>
</tbody>
</table>

(Europe only)

**US Safety Study of Ferric Gluconate: Serious AEs vs Historical Iron Dextran Control**

<table>
<thead>
<tr>
<th>Event</th>
<th>Iron Dextrans (%)</th>
<th>Ferric Gluconate (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life threatening</td>
<td>0.61%*</td>
<td>0.04%</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>23/3768</td>
<td>1/2493</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.36%-0.86%</td>
<td>0%-0.22%</td>
<td></td>
</tr>
<tr>
<td>Drug intolerance</td>
<td>2.47%</td>
<td>0.44%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>64/2589</td>
<td>11/2493</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.87%-3.07%</td>
<td>0.21%-0.71%</td>
<td></td>
</tr>
</tbody>
</table>

CI denotes 95% confidence interval – no overlap.

*93\% reduction in risk of life-threatening reaction with ferric gluconate.

Lack of Ferric Gluconate Cross-Reactivity in Dextran-Allergic Patients

- No relationship between history of iron dextran allergy and risk for adverse events

*Related or unrelated to study drug.

As a result

• Based on these data, overnight most dialysis patients were switched from iron dextran to ferric gluconate and later iron sucrose
Total Reported Serious AEs per Million Doses of 100mg

AEs and IV Iron Therapy

- FDA Medwatch reports (2001-2003) show HWM ID was associated with a 3.4-fold increase in odds of life-threatening AEs
- This analysis likely underestimates AEs with HWM ID and overestimates AEs with LMW ID (All AEs reported by generic name only were attributed to LMW ID)

Relative Safety of Iron Dextran (INFeD, DexFerrum, ImFeron) Preparations

- McCarthy JT, et al.

- Fletes R, et al.

- Chertow GM, et al.

- Mamula, et al.

- Case, G.

- Silverstein, et al.

AEs and IV Iron Therapy: Recent FDA Medwatch Reports

- Obtained from Freedom of Information, all AEs from 1/1/07 to 12/31/09
- Iron dextran
  - HMW ID had 116 AEs; 88 unidentifiable
  - LMW ID had 127 AEs; 75 unidentifiable
  - IMS data base: approximately five times as many doses LMW ID sold during this period
Comparative Studies

- Two prospective: LMW ID and iron sucrose\textsuperscript{1,2}
- One metaanalysis\textsuperscript{3}
- One prospective: Iron sucrose and ferumoxytol\textsuperscript{4}
- One retrospective: all but HMW ID\textsuperscript{5}
- No statistically significant difference in AEs
- One prospective FCM vs IS\textsuperscript{6,7}

4. MacDougall et al. \textit{cJASN} 2014  
6. Onken et al, \textit{NDT} 2013  
7. Quinibi ASN 2007
FDA Review of IV Iron Anaphylactic Reactions

- IMS Database, FDA Adverse Event Reporting System, Death Certificates, ER Visits
- Reactions with all products possible
- Using current system, not possible to determine relative rates of SAE, absent head to head trials
- Spontaneous adverse event reporting cannot and should not be used for this purpose!

Summary of Safety of IV Irons

- AEs occur with all the formulations of IV iron
- Frequency of SAEs from prospective studies is extremely low, but current reporting mechanism tells us nothing about the frequency among available products
- Preponderance of published literature, all retrospective, suggests that HMW ID should be used only with caution
- The NCCN guidelines nJASN proscribe HMW ID and recommend LMW ID when iron is indicated for CIA
Premedication and Serious Adverse Events

- Patients SHOULD NOT be premedicated with diphenhydramine which can cause hypotension, flushing, somnolence and supraventricular tachycardia
- Inappropriate intervention can cause SAE
- Minor chest and back tightness, usually after test dose, first described by Steve Fishbane is NOT a serious AE
- Resolves without treatment: Do NOT intervene with epinephrine or diphenhydramine
- An SAE should consist of hypotension, tachypnea, tachycardia, wheezing, stridor or periorbital edema
- Premedication with steroids only for allergic diatheses

We found that 87% of the 135 patients had no reaction to iron dextran infusion. The rate of adverse reactions was substantially less than that of 25% previously reported among 481 patients who had iron deficiency due to a variety of causes (9). The most common side effect that we observed was sedation after the intravenous infusion of diphenhydramine (Parke-Davis and Warner-Lambert Co., package insert for Benadryl for injection, 1997-1998).
Picture of a Patient with Minor Infusion Reaction to IV Iron
Picture of the Same Patient After 3.5 minutes with Infusion Reaction Resolved
HYPERSENSITIVITY FROM IV IRON DUE TO IMMUNE REACTION

- Immediate:
  - Skin: Pruritis, extended flush, urticaria, angioedema
  - Respiratory: Dyspnea, tachypnea, cough, bronchospasm, stridor
  - GI: Nausea, emesis, colic, diarrhea
  - CV: Hypo & Hypertension, tachy & bradycardia, palpitations, chest pain, shock
  - CNS: Dizziness, syncope, LOC

- Delayed:
  - Fever
  - Arthralgia, Myalgia
  - Lymphadenopathy
  - Exanthems

IV Iron Symptoms Due to Free Iron Toxicity

- Transient facial flushing
- Chest oppression
- Headache
- Nausea, Diarrhea, Metallic taste
- Back Pain
- Low grade fever
- Arthralgia, Myalgia

Comparison of Free and Labile Iron Content in Parenteral Iron Products

Free Iron content in High dose IV Iron products

Labile Iron Pools in Parenteral Iron Products

Blue bars indicate results obtained without pH adjustment. Red bars indicate results obtained following adjustment to pH 7.0

Tryptase Levels After Minor Infusion Reactions

- N=>200 since 2002

- Mean change from baseline 0.0 mg/dl
- Recent publication in Allergy and Immunology\(^1\) reported 36% of patients with diagnosis of “anaphylaxis” had normal tryptase levels
- Earliest levels drawn at one hour
- Concluded that better marker is necessary
- No published data extant describing criteria for diagnosing anaphylaxis in recipients of IV iron
- No publication extant supports anything other than iron infusion reactions when HMW ID is excluded\(^2\) except for
- One published “anaphylactic reaction” with elevated tryptase\(^3\)

\(^1\) Sala-Cunill et al 2013; Allergy and Immunology
\(^2\) Santosh et al 2011; NDT
\(^3\) Novey et al, Ann Allergy;1994;72:224-228
Baseline Mast Cell Tryptase Elevated in Hemodialysis Patients

- Serum mast cell tryptase levels were above 11.4 µg/l (95th percentile) in 84 of 93 patients.
- The intensity of pruritus correlated significantly (p = 0.014) with the tryptase levels, an association not yet shown for other mast cell-related parameters1.
- The minimal increase in acute total tryptase levels considered clinically significant was suggested to be 2 + 1.2 X baseline tryptase levels2.

Role of Dextran Antibodies

- The presence of dextran antibodies prior to ID infusion was not associated with ADRs.
- No increase in antibodies after 9 month course of ID.
- ADRs were not IgE mediated.
- Most normal people have circulating antibodies to dextran.
- Dextran antibodies considered clinically insignificant.

Richter et al 1982; Immunology today 3:132-138
### IDA-301 - Adverse Events

<table>
<thead>
<tr>
<th>AE Category</th>
<th>Ferumoxytol N=608</th>
<th>Placebo N=200</th>
<th>Total N=808</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events n</td>
<td>Subjects n (%)</td>
<td>Events n</td>
</tr>
<tr>
<td>All AEs</td>
<td>718</td>
<td>299 (49.2)</td>
<td>206</td>
</tr>
<tr>
<td>Related* AEs</td>
<td>176</td>
<td>89 (14.6)</td>
<td>25</td>
</tr>
<tr>
<td>SAEs</td>
<td>23</td>
<td>16 (2.6)</td>
<td>6</td>
</tr>
<tr>
<td>Related* SAEs</td>
<td>4</td>
<td>4 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>AEs of Special Interest- protocol-defined¹</td>
<td>26</td>
<td>22 (3.6)</td>
<td>2</td>
</tr>
<tr>
<td>Cardiovascular AE Composite Endpoint²</td>
<td>6</td>
<td>5 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>AEs Resulting in Temporary Discontinuation of Study Drug</td>
<td>4</td>
<td>3 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>AEs Resulting in Permanent Discontinuation of Study Drug</td>
<td>17</td>
<td>12 (2.0)</td>
<td>2</td>
</tr>
<tr>
<td>AEs Resulting in Study Discontinuation</td>
<td>5</td>
<td>3 (0.5)</td>
<td>3</td>
</tr>
<tr>
<td>Death³</td>
<td>2</td>
<td>2 (0.3)</td>
<td>1</td>
</tr>
</tbody>
</table>

1 AEs of Special Interest include hypotension and hypersensitivity as defined in the protocol
2 Cardiovascular AE Composite Endpoint includes myocardial infarction, heart failure, moderate to severe hypertension and hospitalization due to any cardiovascular cause.
3 Reported as unrelated to study drug by the investigator.

* Related AEs are those with relationship classified by investigator as related to study drug. Vadhan-Raj AJH 2013
Primary Endpoint: Safety
Summary of Adverse Events

<table>
<thead>
<tr>
<th>AE Category</th>
<th>Ferumoxytol (N=80)</th>
<th>Iron Sucrose (N=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Subjects N (%)</td>
</tr>
<tr>
<td>All AEs</td>
<td>86</td>
<td>38 (48)</td>
</tr>
<tr>
<td>Related AEs</td>
<td>8</td>
<td>8 (10)</td>
</tr>
<tr>
<td>SAEs</td>
<td>8</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Related SAEs</td>
<td>1</td>
<td>1 (1)</td>
</tr>
<tr>
<td>AEs of Special Interest¹</td>
<td>1</td>
<td>1 (1)</td>
</tr>
<tr>
<td>AEs leading to drug discontinuation</td>
<td>1</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

¹ Includes acute AEs of moderate-to-severe hypotension and hypersensitivity reactions
Personal Communication to both authors

- In Vadhan-Raj’s study an attempt to administer the ferumoxytol over 17 seconds was standard.
- In FIRST administration occurred over a minimum of 60 seconds.
Current Epocrates Section on IV iron therapy

Comments

- If patients cannot tolerate oral iron or have such a rapid iron loss that oral iron cannot keep up with the losses, iron can be given parenterally. (B) Evidence In addition, intravenous iron has shown superior efficacy to oral iron in the treatment of iron deficiency anemia related to malignancy and inflammatory bowel disease. [63] [64] [65].
- About 1% of patients may have an anaphylactic reaction to iron dextran and so a test dose is mandatory.
## Adverse Events

**n=396**

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>22 (5.6)</td>
</tr>
<tr>
<td>Any Serious AE</td>
<td>0 (0)</td>
</tr>
<tr>
<td>AEs resulting in discontinuation</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>AEs requiring intervention</td>
<td></td>
</tr>
<tr>
<td>Decreased infusion rate or temporary interruption alone</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>IV methylprednisolone alone</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Temporary infusion interruption plus IV methylprednisolone</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>AEs occurring in &gt;1 patient</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>7 (1.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Flushing</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (0.5)</td>
</tr>
</tbody>
</table>

Conclusion

- IV iron is safe and effective across a broad spectrum of anemias and much safer than most physicians realize.
- The perception of serious danger is folklore fueled by inappropriate premedication and interventions for self-limited minor infusion reactions and publications using proscribed comparison methodologies.
- Is it possible that reported SAEs with IV iron, when HMW ID is avoided are overwhelmingly iatrogenic?