Intravenous (IV) iron for severe iron deficiency

A nemia affects about one-third of humans; iron (Fe) deficiency is the most common cause. In Canada (2009-11), deficiency defined as serum ferritin < 15 mcg/L was estimated to affect 13% of females aged 12-19, and 9% of females aged 20-49. This estimate is probably low, as the ferritin cutoff is arbitrary and it excludes residents of First Nation reserves, where nutrition is often inferior to the rest of Canada. Iron is essential for oxygen transport by hemoglobin (Hb), but also for energy metabolism, including the mitochondrial electron transport chain. Deficiency without anemia may cause non-specific symptoms (e.g. fatigue, impaired concentration, weakness) and signs (e.g. hair loss, nail and mucosal changes), but there is surprisingly little evidence about whether treatment is beneficial. Identifying the cause is always important. Treatment with oral iron and/or diet is usually simple, although only a tiny fraction of ingested elemental iron is absorbed.

However, sometimes iron must be given parenterally. IV iron can rescue patients unable to tolerate or absorb oral iron, or who lose blood rapidly. Examples include heavy menses, celiac disease, gastric bypass, inflammatory bowel disease, and GI bleeding. When iron repletion is urgent, IV administration saves time, blood transfusion, and money and is underutilized.

This Letter does not discuss controversy over IV iron use for hemodialysis patients.

3 cases illustrate appropriate use

- **Menorrhagia:** A 20 y/o female university student had exertional dyspnea from anemia caused by chronic menstrual blood loss. Her resting heart rate was 126, Hb 70 g/L (120-155), mean cell volume (MCV) 55 fl (82-98), ferritin 2 mcg/L (10-150). She was about to travel overseas, and received 1 g IV iron dextran over 4 hours in preference to red cells. Within 24 days, her Hb was 117 g/L, MCV 71 fl, ferritin 28 mcg/L. Her symptoms resolved and her menorrhagia was addressed.

- **Chronic upper GI bleed and malnutrition:** A 56 y/o homeless man suffered from schizophrenia and alcoholism. He was hospitalized after vomiting blood and collapsing in the street. His initial Hb was 36 g/L, MCV 78 fl, ferritin 20 mcg/L. A large gastric ulcer was treated at endoscopy and he received 3 units packed red cells. Emergency room records revealed chronic iron deficiency anemia for at least 7 years. While hospitalized, he was given 2 g IV iron dextran over 2 days. Two months later, his Hb had risen to 123 g/L, the MCV to 95 fl.

- **Chronic lower GI bleed and limited iron absorption:** A 14 y/o boy with severe ulcerative colitis had daily bloody stools. Concurrent celiac disease limited iron absorption from a vegetarian diet. His Hb was 44 g/L, MCV 58 fl and plasma ferritin < 1 mcg/L. A test dose of iron dextran caused wheezing, back and abdominal pain, but after 25 mg IV diphendehydramine, he tolerated iron sucrose 600 mg. Seven weeks later, his Hb was 120 g/L and MCV 79 fl. Additional iron sucrose compensated for ongoing lower GI bleeding, and his Hb peaked at 143 g/L with a ferritin of 89 mcg/L.

**Indications and Dosing**

Severe iron deficiency plus inability to tolerate or absorb oral iron is the main indication. In the face of ongoing blood loss or urgent surgery, IV iron corrects anemia much faster than oral iron. The bodies of well-nourished people contain about 4-5 grams of elemental iron, half circulating in red cells. The remainder is stored in the bone marrow, liver, and spleen. Adult patients with profound iron deficiency require at least 1 gram of elemental iron to replete body stores. To correct anemia, another 200 mg is required per 10 g/L increment in Hb. The convenience of iron repletion depends on hospital policies for administration, including availability of pre-printed orders.

**Benefits**

Meta-analyses report modest increases in Hb and reductions in transfusion for IV (and oral) iron, but no convincing harms. The modest benefits are explained by trials which enrolled patients with relatively mild iron deficiency, or with chronic conditions limiting hematopoeisis.

**Harms**

Early iron dextran preparations caused frequent anaphylaxis and some fatalities. Although this is now rare, monographs warn of possible anaphylaxis, and against use during active infection, and using iron dextran requires a physician’s presence during a test dose. During 2013-2015 the European Medicines Agency required strengthened warnings about fatal anaphylaxis for all parenteral iron products. Health Canada and the U.S. FDA tightened warnings about fe...
which is officially contra-indicated for people with any drug allergy. Subsequent decreased utilization ended ferumoxytol’s availability in Canada in January 2016. Comparative safety of dextran vs. non-dextran iron cannot be established, because randomized controlled clinical trials (RCTs) are too small for reliable comparison of infrequent serious adverse events, including death. RCTs comparing ferric gluconate, iron sucrose, or ferumoxytol do not establish a difference in incidence of anaphylaxis. Observational studies have not demonstrated a convincing overall safety advantage for any product. A new retrospective FDA analysis of 688,183 U.S. non-dialysis recipients of IV iron between 2003-2013 (dextran, sucrose, gluconate, or ferumoxytol) identified 274 cases of anaphylaxis at first exposure, and 170 more episodes during repeat doses. The probability of an anaphylactic reaction during repletion with 1000 mg Fe appeared least with iron sucrose (21:100,000) and highest with iron dextran (82:100,000). However deaths on the same day as the iron infusion did not differ between preparations (see Table on website). Crude incidence of death numerically favoured iron dextran (4:100,000) over iron sucrose (7-9:100,000), ferric gluconate (6-12:100,000), or ferumoxytol (7:100,000). In dialysis patients, the incidence of fatal or life-threatening adverse events from iron dextran was estimated by the FDA at anywhere from 2 to 300 per million exposures. This risk of harms with red cell transfusion are similar in frequency. 

Table 1: IV iron products available in Canada and their approved indications

<table>
<thead>
<tr>
<th>Product (brand name)</th>
<th>Approved indications</th>
<th>Incidence of hypersensitivity reported in monograph*</th>
<th>Concentration</th>
<th>Price per 100mg Fe**</th>
</tr>
</thead>
<tbody>
<tr>
<td>iron dextran (Dexiron)</td>
<td>iron deficiency when oral iron inadequate</td>
<td>no estimate provided</td>
<td>50 mg/mL</td>
<td>$27.50</td>
</tr>
<tr>
<td>sodium ferric gluconate (Ferrlecit)</td>
<td>iron deficiency anemia of hemodialysis</td>
<td>3.3 per million to at least 6 per thousand</td>
<td>12.5 mg/mL</td>
<td>$44.29</td>
</tr>
<tr>
<td>iron sucrose (Venofer)</td>
<td>iron deficiency anemia in CKD</td>
<td>23 per million</td>
<td>20 mg/mL</td>
<td>$38.15</td>
</tr>
</tbody>
</table>

* these figures cannot be compared directly, as they are based partly on spontaneous ADR reports.
** Vancouver Hospital and Health Sciences Centre pharmacy, January 2016.

Conclusions
- Intravenous iron markedly benefits appropriately selected people with chronic severe iron deficiency.
- Rare but potentially fatal reactions occur with all IV iron products. This requires administration in a setting where immediate treatment is available, including adrenaline.
- No formulation is proven to be safer than others. IV iron is preferable to IM injection.

References


21. Wang, C. US FDA. Personal communication, January 2016. See Table 2 in this Letter.


25. Health Canada Drug Product Database. Product monographs:
   - Sodium ferric gluconate (Ferrlecit): http://webprod5.hc-sc.gc.ca/dpd-bdpp/item-iteme.do?pm-mp=00019077

Table 2: Death Rates on Day of Incident IV Iron Administration in the Non-Dialysis Population*

<table>
<thead>
<tr>
<th>IV Iron</th>
<th># Deaths</th>
<th># New Users</th>
<th>Incidence Rate/per 100,000 persons (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003-2013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron dextran</td>
<td>10</td>
<td>247,500</td>
<td>4.0 (1.9, 7.4)</td>
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<tr>
<td>Iron gluconate</td>
<td>11</td>
<td>94,400</td>
<td>11.7 (5.8, 20.8)</td>
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<tr>
<td>Iron sucrose</td>
<td>19</td>
<td>264,166</td>
<td>7.2 (4.3, 11.2)</td>
</tr>
<tr>
<td>2010-2013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron dextran</td>
<td>3</td>
<td>77,935</td>
<td>3.8 (0.8, 11.2)</td>
</tr>
<tr>
<td>Iron gluconate</td>
<td>2</td>
<td>34,029</td>
<td>5.9 (0.7, 21.2)</td>
</tr>
<tr>
<td>Iron sucrose</td>
<td>12</td>
<td>134,836</td>
<td>8.9 (4.6, 15.5)</td>
</tr>
<tr>
<td>Ferumoxytol</td>
<td>6</td>
<td>82,117</td>
<td>7.3 (2.7, 15.9)</td>
</tr>
</tbody>
</table>

* Courtesy Dr. Cunlin Wang, US FDA, personal communication January 2016