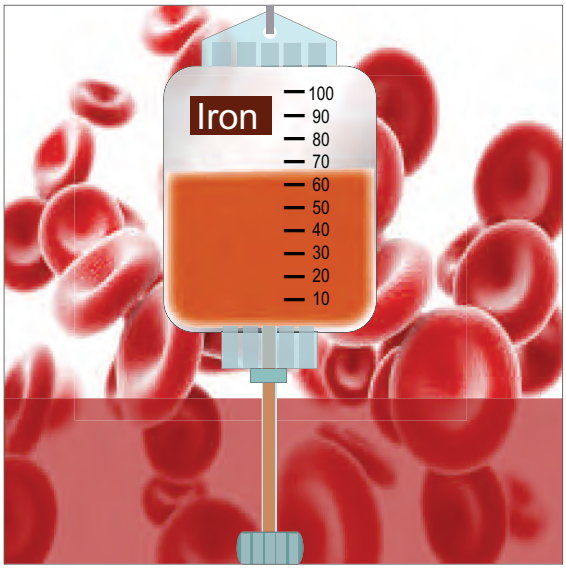
therapeutics letter ©

THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Intravenous (IV) iron for severe iron deficiency



Anemia affects about one-third of humans; iron (Fe) deficiency is the most common cause.[1] 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.[2] 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.[3,4,5] 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.[6,7]

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.[8,9] This Letter does not discuss controversy over IV iron use for hemodialysis patients.[10]

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 diphenhydramine, 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.[11]

Benefits

Meta-analyses report modest increases in Hb and reductions in transfusion for IV (and oral) iron, but no convincing harms.[12-14] 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.[15] Health Canada and the U.S. FDA tightened warnings about ferumoxytol,

Mailing Address: Therapeutics Initiative
The University of British Columbia
Department of Anesthesiology, Pharmacology & Therapeutics
2176 Health Sciences Mall
Vancouver, BC Canada V6T 1Z3

Tel.: 604 822•0700
Fax: 604 822•0701
E-mail: info@ti.ubc.ca
www.ti.ubc.ca

which is officially contra-indicated for people with any drug allergy.[16] 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.[17]

Observational studies have not demonstrated a convincing overall safety advantage for any product.[18,19] 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).[20] 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).[21] 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.[22] **Risk of harms with red cell transfusion are similar in frequency.**[23]

Non-allergic toxicity includes local reactions to the infusate, delayed muscle and joint pains, transient hypotension, and fever. These are generally self-limited. Nothing is known about long-term toxicity. Increased risk of infection after IV iron is not established.

Does premedication or IM injection improve safety?

Premedication is not required, and is not known to prevent dangerous hypersensitivity. IV diphenhydramine 25 mg predictably causes sedation.[24] IM iron injection is not safer, but has the disadvantages of local pain and delayed benefit.

Parenteral iron formulations

Table 1 shows products available in Canada as of February 2016 and their approved indications.[25] While not approved officially for total dose infusion, iron preparations are widely used in Canada for rapid iron repletion. IV is preferable to intramuscular (IM) administration, because IM injections are painful and absorption incomplete.

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.**

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

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

* these figures cannot be compared directly, as they are based partly on spontaneous ADR reports.

** Vancouver Hospital and Health Sciences Centre pharmacy, January 2016.

References

1. Kassebaum NJ, Jasrasaria R, Naghavi M et al. *A systematic analysis of global anemia burden from 1990 to 2010*. Blood. 2014; 123(5): 615-24. DOI: 10.1182/blood-2013-06-508325.
2. Cooper M, Greene-Finestone, L, Lowell H et al. *Iron sufficiency of Canadians. Statistics Canada Health Reports*. 23 (4), November 2012. http://www.statcan.gc.ca/pub/82-003-x/2012004/article/11742-eng.htm
3. Pratt JJ, Khan KS. *Non-anaemic iron deficiency – a disease looking for recognition of diagnosis: a systematic review*. Eur J Haematology 2015; DOI: 10.1111/ejh.12645.
4. Favrat B, Balck K, Breymann C et al. *Evaluation of a single dose of ferric carboxymaltose in fatigued, iron-deficient women -- PREFER a randomized placebo-controlled study*. PLoS ONE [Electronic Resource] 2014; 9(4): e94217. DOI: 10.1371/journal.pone.0094217.
5. Avni T, Leibovici L, Gafter-Gvili A. *Iron supplementation for the treatment of chronic heart failure and iron deficiency: systematic review and meta-analysis*. Eur J Heart Fail 2012; 14(4): 423-9. DOI: 10.1093/eurjhf/hfs017.
6. *BC Guidelines and Protocols Advisory Committee. Iron Deficiency - Investigation and Management*. BCGuidelines.ca June 15, 2010. http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/iron-deficiency
7. Camaschella C. *Iron-Deficiency Anemia*. N Engl J Med 2015; 372(19): 1832-43. DOI: 10.1056/NEJMra1401038.
8. Auerbach M, Adamson J, Bircher A, et al. *On the safety of intravenous iron, evidence trumps conjecture*. Haematologica May 2015; 100(5): e214-5. DOI: 10.3324/haematol.2014.121004.
9. Callum J, Lin Y, Himmel W , Killian M and Helman A. *IV Iron for Anemia in Emergency Medicine*. Emergency Medicine Cases podcast. Episode 65; May 2015. http://emergencymedicinecases.com/iv-iron-for-anemia-in-emergency-medicine/
10. Charytan DM, Pai AB, Chan CT et al. *Considerations and challenges in defining optimal iron utilization in hemodialysis*. J Am Soc Nephrol 2015; 26(6): 1238-47. DOI: 10.1681/ASN.2014090922.

The draft of this Therapeutics Letter was submitted for review to 70 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

The Therapeutics Initiative is funded by the BC Ministry of Health through a grant to the University of BC. The Therapeutics Initiative provides evidence-based advice about drug therapy, and is not responsible for formulating or adjudicating provincial drug policies.

11. Sunnybrook Health Sciences Centre. *Physician's Orders: Intravenous Iron (Venofer, Feraheme) Outpatient Orders*. PR 50006; 2015 Feb 18. http://emergencymedicinecases.com/wp-content/uploads/filebase/pdf/IV_Iron_Outpatient_Orders_Form_PR50006.pdf
12. Gurusamy KS, Nagendran M, Broadhurst JF et al. *Iron therapy in anaemic adults without chronic kidney disease (Review)*. Cochrane Library 2014, issue 12. Art ID: CD010640. DOI: 10.1002/14651858.CD010640.pub2.
13. *Avni T, Bieber A, Grossman A et al. The safety of intravenous iron preparations: systematic review and meta-analysis*. Mayo Clin Proc 2015; 90(1): 12-23. DOI: 10.1016/j.mayocp.2014.10.007.
14. Litton E, Xiao J, Ho KM. *Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomized clinical trials*. BMJ 2013; 347:f4822. DOI: 10.1136/bmj.f4822.
15. European Medicines Agency. *Assessment report: Iron containing intravenous (IV) medicinal products. 2013;* www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/IV_iron_31/WC500150771.pdf
16. Health Canada. *Dear Healthcare Professional Letter: Health Canada Endorsed Important Safety Information on FERAHEME (ferumoxytol). Important Safety Information RA-42607 November 21, 2014*. http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/42607a-eng.php
FDA. *Drug Safety Communication: FDA strengthens warnings and changes prescribing instructions to decrease the risk of serious allergic reactions with anemia drug Feraheme (ferumoxytol)*. MedWatch March 30, 2015. http://www.fda.gov/Drugs/DrugSafety/ucm440138.htm
17. Macdougall IC, Strauss WE, McLaughlin J et al. *A randomized comparison of ferumoxytol and iron sucrose for treating iron deficiency anemia in patients with CKD*. Clin J Am Soc Nephrol 2014; 9(4): 704-12. DOI: 10.2215/CJN.05320513.
18. Brookhart, MA, Freburger JK, Ellis AR et al. *Comparative Short-term Safety of Sodium Ferric Gluconate Versus Iron Sucrose in Hemodialysis Patients*. Am J. Kidney Dis. 2016; 67(1): 119-27. DOI: 10.1053/j.ajkd.2015.07.026.
19. Airy M, Mandayam S, Mitani AA et al. *Comparative outcomes of predominant facility-level use of ferumoxytol versus other intravenous iron formulations in incident hemodialysis patients*. Nephrol Dial Transplant 2015; 30(12): 2068-75. DOI: 10.1093/ndt/gfv305.
20. Wang C, Graham DJ, Kane RC et al. *Comparative Risk of Anaphylactic Reactions Associated with Intravenous Iron Products*. JAMA. 2015; 314(19): 2062-8. DOI: 10.1001/jama.2015.15572.
21. Wang, C. US FDA. *Personal communication, January 2016*. See Table 2 in this Letter.
22. Wysowski DK, Swartz L, Borders-Hemphill BV, et al. *Use of parenteral iron products and serious anaphylactic-type reactions*. Am J Hematol 2010; 85(9): 650-4. DOI: 10.1002/ajh.21794.
23. Callum JL, Lin Y, Pinkerton PH et al. *Bloody Easy 3: Blood Transfusions, Blood Alternatives and Transfusion Reactions. A Guide to Transfusion Medicine (Third Edition)*. Ontario Regional Blood Coordinating Network 2011. http://transfusionontario.org/en/cmdownloads/categories/bloody_easy/
24. Barton JC, Barton EH, Bertoli LF et al. *Intravenous iron dextran therapy in patients with iron deficiency and normal renal function who failed to respond to or did not tolerate oral iron supplementation*. Am J Med. 2000; 109(1): 27-32.
25. Health Canada Drug Product Database. *Product monographs:*
- Iron dextran (Dexiron): http://webprod5.hc-sc.gc.ca/dpd-bdpp/item-iteme.do?pm-mp=00018869
- Sodium ferric gluconate (Ferrlecit): http://webprod5.hc-sc.gc.ca/dpd-bdpp/item-iteme.do?pm-mp=00019077
- Iron sucrose (Venofer): http://webprod5.hc-sc.gc.ca/dpd-bdpp/item-iteme.do?pm-mp=00018889

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

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

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