Title: Parenteral Iron Therapy for Anemia: A Clinical and Cost-Effectiveness Review

Date: 14 February 2008

Context and policy issues:

Anemia is a complication of chronic diseases and commonly occurs in patients with end-stage renal disease. Anemia is defined as a hemoglobin (Hb) level less than 12 g/dl in women and less than 13 g/dl in men. Iron is essential to maintain sufficient Hb levels and has a role in oxygen delivery. Impaired quality of life and cardiac complications occur in patients with chronic untreated anemia. Patients with chronic kidney disease (CKD) are likely to require iron therapy due to increased gastrointestinal (GI) bleed-associated iron loss and platelet dysfunction. Patients with CKD on hemodialysis (HD) also have an increased blood loss from the HD along with associated blood sampling. In addition, CKD patients being treated with erythropoiesis-stimulating agents (ESA) require more iron to for red blood cell production. Oral iron is often not well absorbed in these patients, and therefore, the use of intravenous (IV) iron is necessary. In addition, oral iron is also not well tolerated in patients with GI disorders.

The IV iron therapies available in Canada are iron dextran (Infufer®, DexIron®), sodium ferric gluconate complex (SFGC) (Ferrlecit®) and iron sucrose (Venofer®). In general, use of iron dextran has decreased after the introduction of SFGC and iron sucrose.

There has been recent pressure on hospitals to change formulary listing of parenteral iron products. It needs to be determined whether SFGC is suitable to be listed as the exclusive IV iron preparation or whether there is a need to provide iron dextran and iron sucrose as well. This report examines the comparative clinical safety and efficacy of the three parenteral iron preparations. Economic evaluations will also be discussed.

Research questions:

1. What is the clinical safety and efficacy of SFGC compared to iron dextran or iron sucrose in patients with anemia as a result of CKD or in patients with other types of anemia?
2. What is the cost-effectiveness of SFGC compared to iron dextran or iron sucrose in patients with anemia as a result of CKD or in patients with other types of anemia?

Methods:

A limited literature search was conducted on key health technology assessment resources, including Pre-Medline, Medline, EMBASE, BIOSIS Previews, CINAHL, Pubmed, the Cochrane Library (Issue 1, 2008), UpToDate, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2002 and January 2008, and are limited to English language publications only. Filters were applied to limit the retrieval to health technology assessments (HTAs), systematic reviews, meta-analyses, economic, guideline, randomized controlled trial (RCT) studies, and observational studies.

Summary of findings:

No HTA reports or systematic reviews were identified that compared the safety or efficacy of IV iron preparations. One guideline that used a systematic review method was included. One RCT and five observational studies were identified. Reports were included that compared SFGC to either iron sucrose or iron dextran or both. All included studies investigated the safety of IV iron preparations and no reports were found comparing clinical effectiveness.

Guidelines

An update to the European Best Practice Guidelines (EBPG) for the Management of Anemia in Patients with Chronic Renal Failure was published in 2004. The EBPG II working group contained experts in renal anemia management and based the guidelines on a systematic review of the literature. One researcher reviewed each article and a second researcher reviewed a random selection of articles. The guidelines recommend iron sucrose as the first choice for patients with CKD since it was considered the safest option followed by SFGC. Iron dextran was not recommended because of the risk of serious and life-threatening adverse events; however, if iron dextran is to be used the guidelines recommend that a test dose be administered prior to initiating therapy. These recommendations were evidence level B (evidence from uncontrolled, non-randomized studies).

Randomized controlled trials

An RCT published in 2003 compared the incidence of adverse events to SFGC with those to iron dextran in HD patients. This was a multi-center double blind crossover study. SFGC treatment was compared to placebo as well as a historical control to identify adverse events in patients that received iron dextran. The historical control data was obtained from four studies that reported on adverse events in a total of 3768 patients who received iron dextran. In this study, patients were randomized 1:1 to either receive SFGC at the first treatment session and placebo at their second treatment session (SFGC-placebo group), or they received placebo as their first treatment and SFGC as their second treatment (placebo-SFGC group). Of the 2534 patients, there were 1264 in the SFGC-placebo group and 1270 in the placebo-SFGC group. Overall, 2493 received SFGC and 2487 received placebo (some patients withdrew after their first treatment and therefore only received their first treatment). There was one life-threatening event in the SFGC group (0.04%) and 11 cases of drug intolerance (0.4%). There were two cases of drug intolerance in the placebo group (0.1%) and no cases of a life-threatening event. There was a statistically significant difference in all adverse events reported respectively for
patients on SFGC (3.9%) and those on placebo (2.5%) \( (p = 0.0006) \). Comparing the SFGC group to the historic iron dextran group, there was a significantly higher incidence of drug intolerance events (0.44% versus 2.47%; \( p < 0.0001 \)) and life-threatening events (0.04% versus 0.61%; \( p = 0.0001 \)) in the iron dextran group. The authors concluded that SFGC is safer than iron dextran and that adverse events caused by SFGC are not as severe. A limitation of this trial is that the comparison with iron dextran was done indirectly with an historical control group. This reduces the potential causality between interventions and observed effects.

**Observational studies**

A retrospective study published in 2005 examined hypersensitivity and death due to different parenteral iron preparations.\(^\text{10}\) Data on the reported adverse events from 1997 to 2002 due to use of iron dextran, iron sucrose or SFGC were obtained from the US Food and Drug Administration’s (FDA) Freedom of Information (FOI) database. Information regarding the indication for use of IV iron was not documented in the FOI database. The all-event reporting rate per 100 mg dose equivalents was 29.2 for iron dextran, 10.5 for SFGC and 4.2 for iron sucrose. The all-fatal-event reporting rate per 100 mg dose equivalents was 1.4 for iron dextran and 0.6 for SFGC. There were no all-fatal-events reported with use of iron sucrose. The authors concluded that iron sucrose has the lowest risk for hypersensitivity reactions. A limitation to this study is the fact that the patient population is unknown.

A similar study was published in 2004 on the safety of parenteral iron.\(^\text{11}\) Data regarding adverse events related to parenteral iron from 1998 to 2000 reported to the FDA were obtained from the World Health Organization. The average number of adverse events per patient reported with use of SFGC was 3.6 compared to 3.0 and 3.1 for high molecular weight (HMW) and low molecular weight (LMW) iron dextran, respectively. Compared to the LMW iron dextran, a significant increase in total adverse events was seen with HMW iron dextran [Odds ratio (OR) 5.5, 95% confidence interval (CI) 4.9 – 6.0] and SFGC (OR 6.2, 95% CI 5.4 – 7.2). The OR for death was higher with the HMW iron dextran (OR 3.6, 95% CI 1.4 – 9.4) compared to LMW iron dextran. Treatment with SFGC increased the risk for non-life threatening adverse events (4 – 14 fold increase) compared with LMW iron dextran and the risk for life-threatening adverse events were similar with SFGC and LMW iron dextran. The total reported serious adverse events was 57.9/million doses of 100mg for HMW iron dextran, 49.6 for SFGC and 11.6 for LMW iron dextran. The authors concluded that the incidence in adverse drug events is lower with LMW iron dextran compared to HMW iron dextran and that SFGC has a higher risk of adverse events compared to LMW iron dextran. An important limitation to this report is the lack of information regarding the patient population; it is unknown if these patients were all patients with anemia due to CKD or other disorders. It is also possible that the adverse events are under-reported, as reporting is voluntary.

An update of the 2004 report \(^\text{11}\) was published in 2006 and used data from 2001 to 2003 from the FDA.\(^\text{12}\) Data on adverse events due to iron sucrose were available at this time as it was approved in 2000 by the FDA. HMW iron dextran was associated with a significant increase in total adverse events (OR 3.2, 95% CI 2.7 – 3.8) and life-threatening adverse events (OR 3.4, 95% CI 2.0 – 5.9) compared to LMW iron dextran. Iron sucrose and SFGC were less likely to be associated with total adverse events or life-threatening adverse events. The rate of life-threatening adverse events per million was 11.3 for HMW iron dextran, 3.3 for LMW iron dextran, 0.9 for SFGC and 0.6 for iron sucrose. Compared to the initial study \(^\text{11}\), the rate of adverse events with SFGC was much less in this study, and the authors concluded that this may be due to increased reporting of events when SFGC was first released, which would correspond to the 2004 study. The authors concluded that overall, the rates of adverse events
due to parenteral iron are low, and that the risks are higher with HMW iron dextran and lowest with SFGC and iron sucrose. Limitations to this report are the lack of information regarding the patient population and the fact that all adverse events may not have been reported, as reporting was voluntary.

A retrospective study reported on use of parenteral iron therapy for a variety of conditions, such as anemia due to cancer, GI blood loss, Crohn’s disease and renal disease. There were 112 patients who received parenteral iron over a 5 year period, with a total of 444 infusions. Iron dextran was administered to 85 patients, SFGC to 34 patients and iron sucrose to two patients. Some patients received more than one type of parenteral iron therapy. Iron dextran resulted in adverse events in 14 patients; eight were minor, six were moderate and none were severe. SFGC resulted in adverse events in 5.8% of patients and all were minor. There were no adverse events reported in the iron sucrose group. The authors concluded by recommending a test dose prior to initiating treatment with iron dextran and stated that a test dose is not necessary for SFGC. A limitation to this study is its overall small sample size with 34 patients who received SFGC and only two received iron sucrose. Accordingly, the lack of adverse events reported in the latter group may be reflective of the lack of power to detect adverse events.

Fifty-seven patients with iron deficiency anemia were studied in a 2005 prospective observational study. Iron sucrose and SFGC were administered to patients for a total of 724 infusions (628 with iron sucrose and 96 with SFGC) and both resulted in improvements in laboratory tests for iron parameters. There were rare (n = 3) and minor adverse events reported with the use of SFGC (flushing and hypotension) and no adverse events reported in patients treated with iron sucrose. The authors concluded that iron sucrose and SFGC are equally safe and effective. Limitations to this study are its observational study design, which does provide evidence of causality between the drug used and the event observed, as well as the small sample size.

Economic evaluations

The study that examined adverse events reporting data from the FDA between 2000 and 2003 also reported some cost information. Based on the assumption that 300,000 dialysis patients in the US require IV iron therapy, the use of iron sucrose instead of LMW iron dextran would cost an additional US$210 million. The use of iron sucrose over iron dextran may result in 27 less life-threatening adverse events and six less deaths per year in the US (based on the adverse events reporting rates per million of 0.6 for iron sucrose and 3.3 for LMW iron dextran). The costs would be US$7.8 million per life-threatening adverse event avoided and US$33 million per death prevented with the use of iron sucrose over LMW iron dextran. The authors concluded that the cost to prevent an adverse event is high and that the use of iron sucrose would not be considered cost-effective compared to the use of iron dextran in HD patients. These results are limited by the fact that this is an observational study and there is insufficient detail regarding the methods used for the cost-analysis.

Limitations

Only one RCT was identified on the use of parenteral iron therapy. This study compared SFGC to a historical iron dextran group and therefore there was no direct comparison of SFGC to iron dextran. The remaining studies were observational studies (four were retrospective) which do not control for potential bias and do not prove causality between the interventions and the events. Also, a small sample size was used in some of the observational studies. Three of the studies identified were retrospective reports of adverse events obtained from the FDA. No
information regarding the patient population was available and these studies may have been subject to underreporting as reporting of adverse events was voluntary. Overall, the quality of these studies is low. No studies were identified comparing the clinical efficacy of different parenteral iron preparations and uncertainty remains regarding these findings. From an economic perspective, only one economic evaluation comparing iron sucrose to iron dextran was identified.

Conclusions and implications for decision or policy making:

In summary, evidence for this topic is extremely limited. The one guideline that was identified recommended use of iron sucrose as it was found to have the least incidence of adverse events, followed by SFGC. The use of iron dextran was not recommended. There is currently no evidence on comparative efficacy between the different parenteral preparations for treating anemia in CKD patients. The available evidence supporting the safety of different parenteral iron preparations is of low quality. There was only one RCT identified, which found that SFGC had a lower incidence of adverse events compared to iron dextran. One study found that SFGC had a higher incidence of adverse events compared to LMW iron dextran, however, this was the only study that reached that conclusion, and the follow-up study did not have the same result. HMW iron dextran had a highest incidence of adverse events. Other observational studies concluded that iron dextran had the highest incidence of adverse events followed by SFGC and then iron sucrose. One study found that SFGC and iron sucrose were comparable.

Overall, evidence suggests that iron dextran is the parenteral iron preparation associated with the highest rate of adverse events, compared to iron sucrose and SFGC. Evidence is inconclusive regarding difference in adverse events between iron sucrose and SFGC. From an economic perspective, evidence on the comparative cost-effectiveness of parenteral iron preparations is limited to one cost analysis. It concluded that iron sucrose would not be considered cost-effective compared to iron dextran in HD patients. No economic evaluation on SFGC was identified. Given the limitations of the evidence currently available, long-term clinical and cost-effectiveness studies will be necessary to determine the place of the different parenteral preparations in the management of anemia.

Prepared by:

Lesley Dunfield, PhD, Research Officer
Emmanuel Nkansah, MLS, MA, Information Specialist
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439
References:


