ORIGINAL ARTICLE

Comparative efficacy and safety of intravenous ferric carboxymaltose (Ferinject) and iron(III) hydroxide dextran (Cosmofer) in pregnancy

B Myers FRCP FRCPath[*†], **O Myers**[‡] **and J Moore** MD FRCOG[§]

[*]Haematology Department, Lincoln County Hospital, Lincoln LN2 5QY, UK; [†]Haematology Department, Nottingham University Hospitals, City Campus; [‡]Aberdeen University, King's College, Aberdeen AB24 3FX, UK; [§]Obstetric Department, Nottingham City Hospitals, City Campus, Hucknall Rd, Nottingham NG5 1PB, UK

Summary:

Background: Iron-deficiency anaemia is common in pregnancy, with well-described maternal morbidities. When oral iron therapy has failed, intravenous (IV) preparations are considered. Ferric carboxymaltose (ferinject) is a new IV preparation which can be given quickly. There are no published data on Ferinject use in pregnancy. This study analyses historical data from women given Cosmofer, compared with those given Ferinject in pregnancy, to assess comparative efficacy and safety.

Methods: Pregnant women treated with Cosmofer and Ferinject, were identified from pharmacy records. Records for all cases were reviewed and those which fulfilled inclusion criteria selected. The inclusion criteria included: symptomatic iron-deficient anaemia unresponsive to oral iron; age $\geq$18; second to third trimester; full blood count taken at least once at two, four and/or six weeks post-infusion. Data were collected on the pre-treatment Hb, ferritin, and same data collected at two, four and six weeks after the infusion. Side-effects or adverse reactions were noted for both the Cosmofer and Ferinject patients.

Results: Results were obtained for 92 women (44 received Ferinject and 48 Cosmofer). Pre-infusion Hb and ferritin levels were comparable in the two groups. At two weeks, the mean Hb rise in the Ferinject group was 1.73 g/dL and 1.34 g/dL in the Cosmofer group. At four weeks, the total rise in Hb was 2.57 g/dL Ferinject, 2.34 g/dL Cosmofer. At six weeks the rise was 3.01 g/dL and 3.2 g/dL respectively. No serious adverse events were reported in either group.

Conclusion: Both preparations appear effective and safe, with low risk of serious adverse effects and side-effects.

Keywords: haematology, maternal–fetal medicine

INTRODUCTION

Iron deficiency and iron-deficiency anaemia are common in pregnancy, even in developed countries, occurring in up to 25% pregnant women in Europe.[1] Maternal consequences are well described, and include cardiovascular symptoms, reduced physical, mental and immune function and peripartum reserves.[2,3]

A recent national guideline defines anaemia in pregnancy as: a haemoglobin (Hb) of less than 11 g/dL in first trimester, $<$10.5 g/dL in second and third trimesters and $<$10 g/dL in postpartum period.[4] In addition, concerns about safety and availability of donor blood have promoted avoidance of inappropriate transfusion and use of transfusion-sparing strategies wherever possible. For the majority of women with iron-deficiency anaemia in pregnancy, oral supplements are adequate, but for a significant minority oral iron therapy has failed or is thought inappropriate. This may be due to malabsorption, poor tolerance or non-compliance.

Correspondence to: B Myers
Email: bethan.myers@btinternet.com

Ferric carboxymaltose (Ferinject) is a new intravenous preparation with a near-neutral pH and physiological osmolality which makes it possible to administer high single doses over a short time period, (typically 15 minutes). It is a novel iron complex with a ferric hydroxide core which is stabilized by a carbohydrate shell, allowing controlled delivery of iron within the cells of the reticulo-endothelial system (primarily bone marrow) and subsequent delivery to the iron-binding proteins, ferritin and transferrin.[5] It is administered as a single dose of 1000 mg for total body infusion (TBI) dose. Randomized controlled trials in the postpartum period have shown either non-inferiority[6,7] or superiority[8] to oral ferrous sulphate in the treatment of iron deficiency anaemia, with rapid and sustained increases in Hb. The risk of allergic reaction appears to be exceedingly low with this agent. Cosmofer, an aqueous iron(III)-hydroxide dextran complex, can also provide a TBI with up to 20 mg/kg, but requires administration over at least 5–6 hours per infusion, because of the small risk of allergic reactions.

The different intravenous preparations have not, to date, been compared with each other in pregnancy, and there is very little data on Ferinject use in pregnancy. However, the licence is similar to that for Cosmofer and other intravenous iron

preparations, in that it may be used in the second and third trimesters of pregnancy where indicated, and is contraindicated in the first trimester.

This retrospective study analyses historical data from pregnant women given Cosmofer, compared with those given Ferinject, to assess comparative efficacy and safety.

In this institution, a large teaching hospital, Cosmofer was in standard usage for pregnant women requiring intravenous iron infusion until 2009, as it gave the facility to administer a TBI in one visit. This typically took 5–7 hours, occupying an antenatal bed during this time, and requiring midwifery input throughout and medical presence for at least the first hour. A decision to change to Ferinject, for the same indications as Cosmofer, was based on the following: firstly, that the infusion can be completed in a very short time period, (resulting in reduced bed occupancy, midwifery and medical input), and secondly, the lack of reported allergic reactions to date.

METHODS

Pregnant women treated with Cosmofer between 2005 and 2009, and those treated with Ferinject from 2009 to June 2011, were identified from pharmacy records. Laboratory records for all cases were reviewed and those which fulfilled the inclusion criteria selected. The inclusion criteria were:

(1) The presence of symptomatic anaemia that was iron-deficient (as shown by low ferritin), and which had not responded to oral iron;
(2) Age $\geq$18 years;
(3) In second or third trimester of pregnancy;
(4) Had full blood count taken at least once at two, four and/or six weeks postinfusion.

Doses of up to a maximum of 1000 mg of Ferinject, and similar dosages for Cosmofer were used to provide a TBI dose. Data were collected on the pretreatment Hb, and ferritin, and, where available, the same data collected at approximately two, four and six weeks after the infusion. Not all women receiving either drug had repeated sampling postinfusion, but all had at least one sample taken at timing as above.

Any side-effects or adverse reactions were noted for both the Cosmofer and Ferinject patients.

RESULTS

Results were obtained for 92 women, of whom 44 received Ferinject and 48 Cosmofer infusions. The results are summarized in Table 1 and are discussed below.

Preinfusion haemoglobins and ferritin levels were comparable in the two groups. In total, 72 patients had a full blood count (FBC) taken at two weeks postinfusion, 37 of the Ferinject group and 35 of the Cosmofer group. The mean Hb rise in the Ferinject group was 1.73 and 1.34 g/dL in the Cosmofer group.

Twenty-nine patients had FBC at four weeks postinfusion (12 Ferinject, 17 Cosmofer). The total rise in Hb over the four weeks was 2.57 g/dL in the Ferinject and 2.34 g/dL in the Cosmofer. At six weeks, the number of samples were smaller, taken in 13 women who had received Ferinject and seven of those receiving Cosmofer, the rise was 3.01 and 3.2 g/dL, respectively

No serious adverse events were reported in either group. One patient in each group had minor symptoms: in the Ferinject group a patient complained of faintness and lethargy a few hours after the infusion and one patient in the Cosmofer group had a mild fever during the infusion.

Table 1 **Ferinject study: Hb and ferritin levels pre- and post-IV iron infusion**

Mean Hb levels	Ferinject	Cosmofer
Preinfusion Hb	8.38 g/dL	8.49 g/dL
Preinfusion ferritin	6.0 ng/mL	5.8 ng/mL
Hb rise at 2 weeks	1.73 g/dL	1.34 d/dL
Hb rise at 4 weeks	2.57 g/dL	2.34 g/dL
Hb rise at 6 weeks	3.01 g/dL	3.2 g/dL

Hb, haemoglobin; IV, intravenous

DISCUSSION AND CONCLUSIONS

Intravenously administered ferric carboxymaltose has been shown to be effective in the treatment of iron-deficiency anaemia in randomized, multicentre trials in other patient populations, including those with inflammatory bowel disease, heavy uterine bleeding in addition to postpartum iron deficiency anaemia and those with chronic kidney disease. To our knowledge, however, this is the first reported study on the use of Ferinject in pregnancy, and the first study to compare the use of two intravenous iron preparations in the pregnancy setting.

Both intravenous iron preparations appear effective and safe in this group of patients, with low risk of serious adverse effects and side-effects.

With regard to efficacy, the results of this small study suggest that Ferinject may produce a faster rise in haemoglobin than Cosmofer. Although larger studies are needed to investigate this further, there is support for this possibility from a study by Beshara *et al.*[9] This is a red cell utilization study comparing distribution of intravenous iron over four weeks of the hydroxide-polymaltose formulated intravenous iron (Ferinject), compared with distribution pattern of intravenous iron-sucrose. In both cases, intravenous iron was distributed to the liver, spleen and bone marrow, but a larger proportion of the complex was quickly distributed to the bone marrow in the polymaltose formulation, with the major portion of the injected dose rapidly distributed to the bone marrow. This may therefore translate into more rapid red cell production.

Regarding safety, intravenous administration of iron preparations has been associated with oxidative stress.[10,11] However, at therapeutic doses, ferric carboxymaltose should not trigger iron-induced lipid peroxidation in the parenchyma, as iron from ferric carboxymaltose is predominantly deposited in the reticulo-endothelial system. A study in rats demonstrated that equivalent doses of available intravenous iron preparations (ferric carboxymaltose, both high-molecular-weight and low-molecular-weight iron dextran, sodium ferric gluconate and iron sucrose) differed in their haemodynamic, oxidative stress and inflammatory responses in hearts from that of normal rats.[12] Ferric carboxymaltose and iron sucrose showed a better safety profile than the other intravenous iron preparations. The Beshara paper suggests that the reticulo-endothelial uptake, especially in the spleen, may reflect the safety of the polysaccharide complexes.

The higher cost of the Ferinject preparation is, at least to some degree, offset by reduction in bed occupancy, midwifery and

medical time input, with the significant patient benefit of TBI in 15 minutes.

The limitations of this study include the fact that it is retrospective and there may be bias in case selection. We attempted to minimize this by including all cases that fulfilled the criteria, for both groups. Very small and unequal numbers in the six-week post-treatment group limit interpretation at this time frame. As this is a small study, uncommon adverse events may be missed.

In conclusion, Ferinject appears a safe and effective product for use in pregnancy with the significant aspect of speed of delivery of the product, and minimal allergic risk compared with Cosmofer. It also shows promise in terms of rapid marrow delivery and response.

DECLARATIONS

Competing interests: BM has received a speaker's fee to present a pregnancy guideline on iron deficiency at a meeting funded by Pharmacosmos.
Funding: This study did not receive any funding.
Ethical approval: This study did not require ethical approval as it was an audit with no contact with or involvement of patients.
Contributorship: BM and JM conceived the study. OM was involved in data analysis. BM wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

REFERENCES

1 WHO Global Database on Anaemia, de Benoist B, McLean E, Egli I, Cogswell M. Worldwide Prevalence of Anaemia 1993–2005. Geneva: WHO Press, 2008. See http://whqlibdoc.who.int/publications/2008/9789241596657_eng.pdf (last checked 15 March 2012)
2 Ekiz E, Agaoglu L, Karakas Z, Gurel N, Yalcin I. The effect of iron deficiency anemia on the function of the immune system. *Hematol J* 2005;**5**:579–83
3 Haas JD, Brownlie T IV. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. *J Nutr* 2001;**131**:676S–90S
4 Pavord S, Myers B, Robinson S, Allard S, Strong J, Oppenheimer C. and on behalf of the British Committee for Standards in Haematology. UK guidelines on the management of iron deficiency in pregnancy. *Br J Haematol* 2012;**156**:588–600
5 Lyseng-Williamson KA, Keating GM. Ferric caroboxymaltose: a review of its use in iron-deficiency anaemia. *Drugs* 2009;**69**:739–56
6 Van Wyk DB, Martens MG. Intravenous ferric carboxymaltose compared with oral iron in the treatment of post partum anaemia: a randomized controlled trial. *Obstet Gynecol* 2007;**110**:267–78
7 Breymann C, Gliga F, Bejenariu C, Strzhova N. Comparative efficacy and safety of intravenous ferric carboxymaltose in the treatment of post partum iron deficiency anemia. *Int J Gynecol Obstet* 2007;**101**: 67–73
8 Seid MH, Derman RJ, Baker JB, Banach W, Goldberg C, Rogers R. Ferric carboxymaltose injection in the treatment of postpartum iron deficiency anemia: a randomized controlled clinical trial. *Am J Obstet Gynecol* 2008;**199**:435.e1–435.e7
9 Beshara S, Sorensen J, Lubberink M, *et al.* Danielson and Hans Lundqvist Pharmacokinetics and red cell utilization of 52Fe/59Fe-labelled iron polymaltose in anaemic patients using positron emission tomography. *Br J Haematol* 2003;**120**:853–9
10 Danielson BG. Structure, chemistry, and pharmacokineticsof intravenous iron agents. *J Am Soc Nephrol* 2004;**15**(Suppl 2):S93–8
11 Agarwal R. Iron, oxidative stress, and clinical outcomes. *Pediatr Nephrol* 2008;**23**:1195–9
12 Toblli JE, Cao G, Oliveri L, *et al.* Evaluation of intravenous iron preparations on cardiovascular toxicity in normal rats [abstract no. PUB476]. American Society of Nephrology Renal Week, 4–9 November 2008, Philadelphia (PA)

(Accepted 15 January 2012)