Canadian Agency for Drugs and Technologies in Health

HTA

HEALTH TECHNOLOGY INQUIRY SERVICE (HTIS)

Title: **Heme Iron Polypeptide (Proferrin®) versus Oral and Injectable Iron Products for the Treatment of Anemia**

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Context and policy issues:

Anemia is common in patients with chronic kidney disease, and is associated with significant morbidity.[1] Complications associated with anemia include an increased rate of hospitalization, decreased quality of life, decreased energy capacity, left ventricular hypertrophy, congestive heart failure, and increased mortality.[1] Controlling anemia has been shown decrease mortality, cardiac complications, hospitalizations, and improve exercise capacity and quality of life.[1,2] Iron is essential for the synthesis of hemoglobin, the protein in red blood cells responsible for the transport of oxygen throughout the body. Use of recombinant human erythropoietin (rHuEPO), a hormone that stimulates red blood cell production, facilitates maintenance of target hemoglobin levels when sufficient iron is present.[3]

In patients undergoing chronic dialysis, iron deficiency is caused by blood loss during the dialysis procedure, increased erythropoiesis (red blood cell production), and insufficient absorption of iron from the gastrointestinal tract.[3] The loss of blood is relatively mild among patients with non dialysis-dependent chronic kidney disease (ND-CKD) and patients with peritoneal dialysis-dependent chronic kidney disease (PD-CKD).[3] In these patients, the administration of oral iron may be adequate to support erythropoiesis as well as to replace any possible ongoing blood loss.[4,5] By comparison, despite ongoing oral iron therapy in most hemodialysis-dependent chronic kidney disease (HD-CKD) patients (even those participating in a rigorous protocol with strict attention to compliance), results from three randomized controlled trials indicate that anemia fails to correct, thereby indicating the need for intravenous (IV) iron.[6-8] Based on evidence from these clinical trials current guidelines recommend IV as the preferred route for iron administration in patients with HD-CKD.[2] Tests commonly used to guide iron therapy in CKD associated anemia include transferrin saturation (a primary indicator of a patient's ability to respond to rHuEPO), hematocrit (a measure of the percentage of red blood cells), and serum ferritin concentration (an indicator of iron stores).[2]

Table 1 provides a list of different iron formulations currently available in Canada for the treatment of anemia. Oral iron salt preparations contain varying amounts of ferrous iron, and the frequency of gastrointestinal (GI) side effects related to each different preparation tends to be directly related to the content of ferrous iron.[9] Approximately 10-20% of patients may complain of nausea, constipation, stomach cramping and/or vomiting after taking oral iron preparations.[9] Compliance is often an issue with iron salts as optimal absorption occurs on an empty stomach (which usually increases the frequency of GI side effects), and they must be taken separately from many medications (e.g. tetracycline, levothyroxine, and antacids) and calcium containing foods or supplements. IV iron preparations have been associated with acute reactions including abdominal pain, nausea, vomiting, fever, musculoskeletal pain, chest pain, shortness of breath, flushing, rash, hypotension, injection-site reactions including phlebitis, and anaphylactic-like reactions.[3] Most of these adverse effects are primarily related to the size of dose and rate of infusion. Data from adverse event reporting and post-marketing studies suggest that ferric gluconate and iron sucrose are safer alternatives compared to iron dextran, but are more expensive.[10]

In May 2007, Medical Futures Inc, received approval from Health Canada to market Proferrin®, a new oral iron supplement termed heme iron polypeptide (HIP), for the treatment of iron deficiency and anemia.[11] HIP has been widely used in the US for the treatment of iron deficiency and anemia due to acute and chronic diseases since 2001.[12] HIP is produced by hydrolysis of bovine hemoglobin.[13,14] Heme is absorbed through a receptor that is different from the absorption mechanism for iron salts.[14] Some potential advantages of HIP over iron salts include a proposed lack of dietary and drug interactions as well as a reduction in GI adverse effects. [12,13] As a relatively expensive alternative, considering the overall impact of HIP in terms of clinical outcome, long-term safety and efficacy, and cost is necessary in order to help guide its use. The available evidence for the clinical and cost-effectiveness of HIP in comparison to other forms or iron replacement for the treatment of anemia will be discussed.

Table 1: Iron Preparations Available in Canada for Treatment of Anemia†

Drug	Amount of Elemental Iron
Oral Iron Salts*	
Ferrous Sulfate (Apo-Ferrous Sulfate®, Novo-Ferrosulfate)	60mg/300mg tablet
Ferrous Gluconate (Apo-Ferrous Gluconate®, Novo-Ferrogluc)	35 mg/300 mg tablet
Ferrous Fumarate (Palafer®)	100 mg/300 mg capsule
Oral Heme Iron Formulation	
Heme Iron Polypeptide (Proferrin®)	11 mg/ tablet
Intravenous Iron	
Iron Dextran (Infufer®, Dexiron™)	50 mg/mL
Sodium Ferric Gluconate Complex (Ferrlecit®)	12.5 mg/mL
Iron Sucrose (Venofer®)	20 mg /mL

† Based on a listing from the Drug Product Database of drugs currently licensed for sale by Health Canada.[15]

***** Preparations in combination with ascorbic acid for increased absorption are also available.

Research questions:

1. What is the comparative efficacy, safety and cost-effectiveness of heme iron polypeptide (Proferrin®) with oral iron products for the treatment of anemia?

2. What is the comparative efficacy, safety and cost-effectiveness of heme iron polypeptide (Proferrin®) with injectable iron products for the treatment or maintenance of anemia in patients with chronic renal failure, with or without dialysis?

Methods:

A limited literature search was conducted on key health technology assessment resources, including The Cochrane Library (Issue 3, 2007), Ovid: EMBASE and Medline, 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 2003 and the present, and are limited to English language publications only. Bibliographies of reports were scanned to identify other relevant evidence.

Summary of findings:

No health technology assessments, systematic reviews, or economic evaluations were retrieved specifically for HIP. Two small randomized controlled trials and one observational trial are discussed below.

Before being marketed in the US, Seligman *et al*., conducted an absorption study comparing HIP with ferrous fumarate or placebo.[13] Fourteen healthy subjects were given a standard breakfast and randomly assigned to three different preparations of 20 mg of HIP, 20 mg of ferrous fumarate or placebo in a double-blind fashion. Mean change in serum iron was measured at 3 hours and 6 hours post ingestion. Iron absorption with HIP was significantly higher when taken with a meal compared to ferrous fumarate or placebo ($p<0.03$ and $p>0.02$, respectively). This suggested that in contrast to iron salts, HIP absorption was not decreased by food and could potentially be taken with or without meals. A similar comparison in fasting state would have been useful to confirm this assumption. After 6 hours, iron absorption was lower for both groups possibly due to a diurnal variation of serum iron. The authors performed a sub-group analysis of patients according to starting ferritin values above and below 50 ng/ml (a value used to establish decreased iron stores in those at risk for anemia). At 3 hours, the low ferritin group had statistically higher serum iron levels with HIP when compared to placebo ($p<0.01$) or ferrous fumarate ($p<0.02$). In the high ferritin group, the difference in iron levels between HIP and placebo was not statistically significant ($p=0.4$) indicating that iron absorption from HIP is regulated. Side effect data was obtained by questionnaire in a double-blind fashion following the 6 hour blood draw. Besides complaints of hunger due to the 6h fast, only two subjects in the ferrous fumarate group complained of heart burn. In a separate study, 10 nonanemic females with a serum ferritin below 50 ng/mL were selected to determine if HIP given as a 60 mg dose of elemental iron would result in markedly increased absorption as compared with the 20 mg dose.[13] Results indicated that serum iron levels did not differ significantly between the 60 mg and 20 mg dose. This, suggests that continual supplementation would not be expected to result in iron overload.

Nissenson *et al.* conducted an open-label randomized controlled trial (n=68) in patients with stable HD-CKD on maintenance IV iron and rHuEPO therapy.[16] Three months of baseline data were obtained to confirm that hematocrit (HCT), serum ferritin, and transferring saturation (TSAT) values were at target levels as recommended by guidelines. Patients were randomized to continue treatment with their respective clinic's IV iron protocol (not specified) or switched to therapy with HIP (at a dose of 21 mg or 36 mg daily) for a period of 6 months. Serum iron level, HCT and rHuEPO and IV iron dose were determined every third month. Each patient was given a monthly questionnaire to ascertain GI side effects. After 6 months, 9 out of the 37 patients on HIP therapy dropped out of the trial. Of these, three subjects discontinued because of GI side effects and one subject due to insufficient iron supplementation. The remaining 5 patients discontinued because of unrelated complications or protocol violation. Adverse effects or study withdrawals in the IV group were not described.

No significant changes were observed in mean TSAT or HCT in the HIP group when compared to baseline after 6 months. A significant reduction in average serum ferritin level was observed at months 4 through 6 (-106 ng/ml; p=0.0014). While the average serum ferritin level of 446ng/mL was still within the guideline target of >100 ng/mL, longer studies are needed to determine if this trend may continue. Although a decrease was observed in average monthly rHuEPO dose during the course of the study, it was not statistically significant. However, the authors noted the fact that rHuEPO dose did not increase in the HIP group to maintain HCT in the target range was an important finding. rHuEPO efficiency, defined as total weekly rHuEPO dose/Hemoglobin was also evaluated. Among subjects administered IV iron, no significant change in average monthly rHuEPO dose or efficiency was noted. Conversely, in the HIP group, significant improvement in efficiency was observed between baseline and months 4 to 6 of the study (p=0.04). Furthermore, when the authors analyzed the high- and low-dose groups separately, there was significant improvement in rHuEPO efficiency in the high-dose HIP group (p=0.016) but not in the low-dose group. In addition, small but significant increases in HCT (p=0.04) and reductions in average monthly rHuEPO doses (p<0.03) during the 6 month period were observed in the high dose group. These results indicate that a higher dose may be more effective in HD-CKD patients. However, methodological flaws in the trial including uncertainty in the randomization procedure, lacking comparative information on the safety and efficacy of IV iron, significantly higher (p<0.02) baseline rHuEPO doses in the oral iron treatment group, a high dropout rate in the oral treatment group, lack of intention-to-treat analysis, and an undefined IV iron treatment protocol render the results of this trial difficult to interpret.

In an unpublished abstract, Ghadder *et al.* examined 12 patients with stable PD-CKD in an observational study.[17] Three months of baseline data were collected including HCT, serum iron indices, and monthly rHuEPO and IV iron dose. Patients discontinued IV iron supplementation and were given 24 mg of HIP twice daily for 4 months. A side-effect questionnaire was administered during the baseline period and once monthly while on HIP therapy. Results revealed no significant changes in HCT, TSAT or ferritin with HIP after 4 months. Average monthly rHuEPO dose decreased significantly during the first two months (-16,669 units/month, p=0.15) when compared to baseline but the difference was not significant at the end of the 4 months. One subject was removed from the study because his TSAT went above the level recommended by guidelines. Significantly less GI side effects occurred with HIP therapy compared with baseline (p=0.03).

Conclusions and implications for decision or policy making:

In summary, the available evidence for HIP evaluation is very limited. Only low quality evidence from small short-term trials currently exists. There is no evidence for efficacy in other forms of anemia. Results indicate that HIP may be a promising alternative to IV iron for patients with chronic kidney disease receiving rHuEPO therapy. Results from an ongoing randomized control trial comparing oral HIP with IV iron sucrose in ND-CKD patients will help determine its efficacy in this population.[18] Given current cost constraints, well designed randomized controlled trials comparing HIP with other iron products for clinically important outcomes including anemia-related complications, rate of hospitalization, and mortality are required to fully assess clinical and economic benefit. Previous economic evaluations have indicated that based on a reduction in rHuEPO dose, HD-CKD patients are more economically treated with IV iron than oral iron salts.[19-21] It would be interesting to determine if this applies with HIP therapy. Until higher quality evidence is available, the decision of when to use one form of iron administration over another in must be based on costs specific to the particular institution and on clinical experience. While the formulation of HIP available in Canada does not require a prescription, some extended health insurers may cover the item when ordered by a physician. Practical considerations, including the out-of-pocket costs to patients and the inconvenience of taking additional oral medication,, may be important determinants of the diffusion of HIP into clinical practice.

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