Iron polymaltose use in chronic kidney disease patients: one unit's experience

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Abstract

Background: A major concern of iron therapy is the safety and related adverse events, in particular, the association of iron therapy to anaphylactic reactions.

Aim: To report adverse reactions to iron polymaltose infusions experienced by patients with chronic kidney disease (CKD) who were not on dialysis and to evaluate the effectiveness of the current iron infusion protocol and dose in achieving target levels for ferritin and transferrin saturation (TSAT).

Methods: Retrospective review of iron infusion adverse events among patients (n =260) with CKD at an Australian metropolitan hospital renal service for the period 2005-2007. Data was collected from the Renal Anaemia Management Database (RAM) and patient medical records, entered into EXCEL for descriptive analysis.

Results: 503 iron polymaltose infusions were delivered to 260 patients with CKD over a 3 year period. Iron polymaltose infused at low dose and slowly administered is safe and well tolerated by most patients. There were no anaphylactic reactions, and only 7 patients experienced mild reactions. Over the 3 year period a greater number of patients achieved target levels for ferritin and TSAT level and improved haemoglobin (Hb) levels.

Conclusion: Using iron polymaltose at the current rate and dose is safe and an effective way to improve ferritin and TSAT levels for CKD patients who attend an outpatient clinic.

Key words:
iron polymaltose, iron deficiency, anaemia, chronic kidney disease

Introduction

A frequent symptom seen in patients with chronic kidney disease (CKD) is anaemia, which has been directly linked with left ventricular dysfunction, heart failure, reduced exercise capacity and reduced quality of life (McMahon, 2008). Iron deficiency is common in CKD patients due to various factors such as reduced dietary intake, impaired absorption, blood losses and chronic inflammation (Horl, 2007). The increased iron requirements during erythropoietin replacement therapy (ERT) are a major cause of iron deficiency which, in itself, is the major cause of poor response to ERT (Johnson, Pollock & MacDougall, 2007). It is essential for patients on ERT to receive iron therapy to support the requirements of increased erythropoiesis, whereas some patients not yet receiving ERT can achieve adequate Hb levels using iron therapy alone (Silverberg et al, 1996; Mircescu, Garneata, Capusa & Ursea 2006; Horl, 2007; Tagboto et al, 2008; Madore et al 2008). ERT and iron replacement have become an integral part of anaemia management.

The major concerns of iron therapy are safety and adverse events, in particular, the association of iron therapy with anaphylactic reactions (Madore et al 2008). There is vast literature available on the various iron preparations and the differences in their safety, with the focus on the incidence of anaphylactic reactions, despite its relative infrequency (Yee & Besarab, 2002; Chertow et al, 2004; Horl, 2007). Literature on iron polymaltose, which is widely used in Australia, is minimal compared to other iron preparations. Dosing and rates of infusion vary greatly and is described in the literature review.

Literature Review

Newman, Ahmed, Thornton and Gibson (2006) reported on the administration of 401 iron polymaltose infusions to 386 patients, in various doses ranging from 800-2350 mg (mean dose = 1338 mg). Infusions were administered in 500 ml of 0.9% sodium chloride and commenced at 40 ml/hr under the direct supervision of a medical practitioner for the first 15 minutes. If there were no observed adverse reactions after the first 50 ml of the infusion, the rate was increased to 120 ml/hr. A premedication was used in 33% of patients. Reactions were seen in 22 patients (5.7%), the most common being rash (n= 6) and nausea/light headedness (n=5). The infusion was stopped for 6 patients. There were no cases of anaphylaxis or anaphylactoid reactions. These authors concluded that iron polymaltose administration was safe and well tolerated and that the use of a premedication and medical monitoring for the first 15 minutes was unnecessary.

Zyl-Smit and Halkett (2002) administered iron polymaltose to 62 haemodialysis patients. Dosage requirements ranged from 900-3,200 mg of iron polymaltose which was diluted in 500 ml of 0.9% sodium chloride

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and infused over a 4 hour period. The majority of patients were not receiving ERT therapy. Hypotensive episodes did occur but were not well described. The authors stated that assessing hypotensive episodes during haemodialysis was difficult, as these events occurred frequently during a normal haemodialysis session. They suggested that all hypotensive episodes were considered unrelated to the iron infusions. Finally, according to these authors iron polymaltose can be used safely and effectively to correct iron deficiency and improve Hb even when used without ERT therapy.

The slower, lower dose infusion is supported by Mcdougall (2006) who found reactions are generally encountered when a high dose of iron is administered too quickly, in particular for milder anaphylactic reactions. Many patients, after experiencing a reaction, can be successfully rechallenged with a lower dose administered more slowly.

Saunders et al (2007) described two groups of haemodialysis patients receiving maintenance doses 100-200 mg or replacement doses 500-1000 mg of intravenous iron polymaltose infusions. A total of 169 patients received 529 infusions of various doses. There were 102 infusions greater than 500 mg. Adverse reactions (n=32), hypotension (21), febrile reactions (4), flushing (3), headache (2) occurred more frequently in the replacement dose group. These authors again reported that hypotensive episodes were unrelated to the iron infusions, however the dose administered to these patient was not stated.

Aim

The purpose of this retrospective review was twofold:

1. To report any adverse reactions to iron polymaltose infusions experienced by CKD patients not on dialysis
2. To evaluate if the current iron infusion dose can achieve and maintain parameters for iron stores, ferritin and TSAT, within current practice guidelines set to optimise erythropoietin therapy in CKD patients.

Sample

All patients with CKD under the care of a nephrologist at a large metropolitan hospital renal service for the period 2005-2007 were included in the review. Simple demographic data was collected on 260 patients and this included gender and date of birth. Iron infusions were being administered for iron deficiency anaemia irrespective of stages of CKD. It was therefore considered irrelevant to collect stages of CKD data for this review. Iron deficiency was established according to Ferritin and TSAT levels recommended by the Caring for Australians with Renal Impairment (CARI) guidelines (Roger, 2006). Iron infusions were administered to 129 female and 131 male patients. The age of patients ranged from 17 to 95 years with an average age of 70 yrs.

Procedure

Patients were referred by the nephrologist to the anaemia coordinator for patient education and referral to the ambulatory [day] care unit where the iron infusions took place. Iron polymaltose infusion protocol was developed according to manufacturer product information and CARI guidelines (Roger 2006). This protocol has been used for several years in this unit, and was last updated and approved by the hospital pharmacy (October 2006) for all renal patients in this hospital (see diagram 1). Iron therapy was administered to patients both pre ERT and also for patients currently receiving ERT when indicated based on biochemistry and haematological results. All patients were asked to report any adverse reaction to the anaemia coordinator, in particular any event that may have occurred following the infusion. Adverse events during the infusion were recorded in the patient's medical record by the ambulatory care staff. To evaluate the effectiveness of the current dose of iron polymaltose, data was collected using the Renal Anaemia

Diagram 1: Hospital Iron Polymaltose Infusion Protocol (Infusion rate section only)

Iron polymaltose (Ferrosig® Sigma Pharmaceuticals) 500 mg administered in 500 ml of 0.9% saline using the following infusion rate protocol

1. 60 ml/hour for 30 minutes
2. 120 ml/hour for 30 minutes
3. 150 ml/hour for the remainder of the infusion

Table 1 Adverse Reactions Reported.

Year	Total Infusions	Number of patients with reaction	Adverse Reactions	Timing of reaction	Infusion ceased
2005	100	2	urticaria	Post infusion	No
2006	175	1	Nausea	Post infusion	No
		1	Nausea & vomiting	Post infusion	No
2007	228	1	Nausea & itching	Post infusion	No
		1	Hypotension	Within 1 hour of infusion	Yes & recommenced
		1	Burning sensation neck, scalp & groin	Post infusion	No

Management Database (RAM) on the following parameters: TSAT; ferritin level; Hb; and ERT dose. The RAM database is an observational database used in our unit since 2001 and is sponsored by Janssen Cilag. The medical records were then reviewed for patients with reported adverse events.

Patients who have experienced any adverse reactions can be challenged with iron sucrose after approval by the consulting nephrologist. Iron sucrose is considered a safer alternative for patients who have experienced reactions to other intravenous iron products because it has markedly fewer incidences of adverse reactions. (Yee & Besarab 2002; Madore et al 2008)

Data Analysis

Data was collected from RAM and patient medical records and were recorded in a Microsoft EXCEL spreadsheet. Simple descriptive analysis was undertaken.

Results

503 iron polymaltose infusions were performed on 260 patients. Most patients received 1-3 infusions over the 3 year period. Seven (7) patients required 6 or more iron infusions mostly due to gastrointestinal blood loss which was being investigated. Over the 3 year period, 7 patients (2.7%) were identified as having some adverse reaction during or post iron polymaltose infusion (Table 1). There were no anaphylactic or life threatening reactions. Reactions occurred more frequently in female patients (6 female: 1 male).

In 2005, two patients experienced urticaria post infusion. Both patients had received iron polymaltose infusions in the past 12 months at the same dose and rate. Both patients have since received uneventful iron sucrose infusions. In 2006, two patients reported nausea and vomiting after receiving their first infusion. One of these patients reported nausea that continued for several days post infusion. Both patients were re-challenged with iron polymaltose. Symptoms re-occurred after the subsequent infusion and therefore both patients were changed to iron sucrose infusions with no adverse symptoms.

Figure 1 Pre Dialysis patients mean Hb g/L

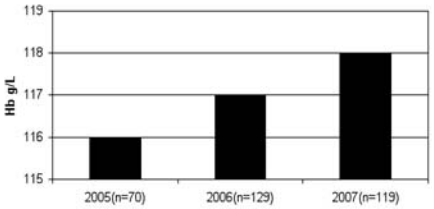
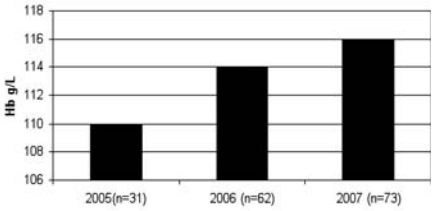


Figure 2 Mean Hb g/L Pre Dialysis Pts on ERT



In 2007, one patient reported nausea and itching post infusion. This patient had previously received uneventful iron polymaltose infusions. Iron sucrose was then administered with no further reactions. Another patient experienced hypotension within 1 hour of commencing their first iron infusion. The infusion was stopped and a medical officer called. The infusion was recommenced at a slower rate and completed with no further events. A third patient reported a burning sensation of the neck, scalp and groin following the first iron polymaltose infusion. This patient has since commenced haemodialysis and has received a lower dose iron polymaltose infusion (100 mg) with no adverse events reported.

Mean Hb for all CKD patients increased over the 3 year period. In 2005 the mean Hb was 116 g/L this increased in 2006 to 117 g/L and to 118 g/L in 2007 (Figure 1). For patients receiving ERT there was an increase in mean Hb over the 3 year period from 110 g/L to 116 g/L (Figure 2).

Average doses of ERT for both drug therapy types increased from 2005 to 2006 (figure 3). The mean dose of Epoetin alfa increased from 6000 to 7150 IU and for Darbepoetin alfa from 33 to 34 µg. This increase may be the result of increasing number of patients on ERT in 2006 (n=62) compared to 2005 (n=31). From our department records, there was an increase of 8.8% in the number of patients to the renal outpatient service in 2006, this includes new patients. New patients being initiated on ERT require higher dosages to achieve target Hb. Once target or required Hb has been achieved doses or frequency of dosing may be reduced (Eprex® Consumer Medicine Information, 2008; Aranesp® Product Information, 2007; Pollock & McMahon, 2005). In 2007 there was a much smaller increase in the number of patients on ERT (n=73). The mean dose for both therapy types decreased, Epoetin alfa 6400 IU and Darbepoetin alfa 33µg while at the same time Hb levels increased from 114 g/L to 116 g/L.

Prior to commencing ERT, CARI guideline recommend that Ferritin level be greater than 100µ/L and TSAT level >20%. For patients on ERT optimisation of therapy is achieved when serum ferritin is between 200-500 µ/L and TSAT level is between 30-40 % (Roger, 2006). Parameters for both ferritin level (Figure 4) and to a lesser extent TSAT level (Figure 5) improved over the 3 year period, with increasing number of patients meeting CARI guidelines target ranges for iron stores.

Discussion

The effectiveness of parenteral iron in supporting ERT has been well established in the literature and reflects the current findings (Besarab, 2000; Roger, 2006; Johnson et al, 2007). From 2005 to 2007, the total number of iron infusions being administered in this unit doubled, the main reason being the move of the Ambulatory Care Unit to a larger facility, increasing the amount of infusions that could be administered per day.

Given the relative cost of using ERT to correct anaemia (Tonelli et al, 2003), it is vital to maintain adequate iron stores for patients on ERT therapy to optimise response.

Figure 3 ERT Average Doses

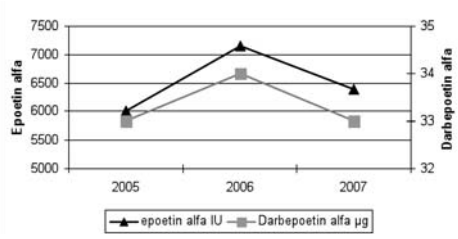
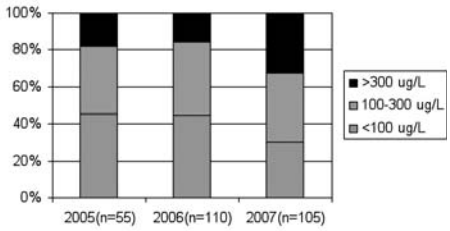


Figure 4 Pre Dialysis Ferritin Level



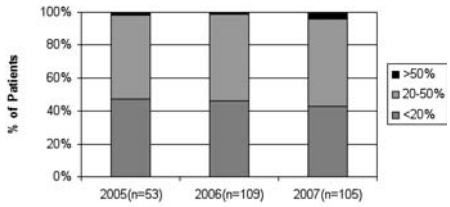
In August 2008, MIMS online state the cost of the two iron products used in this unit to be:

1. Ferrosig®, iron polymaltose, 100mg/2mls (5) $51.90 per box
2. Venofer®, iron sucrose, 100mg/5mls (5) $138.87 per box.

The current lower dosage and slower administration protocol may have resulted in fewer adverse reactions to iron polymaltose infusion than previously reported in the reviewed literature (Mcdougall, 2006). Johnson et al (2007) and Madore (2008) reported reactions to intravenous iron such as hypotension, dyspnoea, arthralgia, myalgia, nausea and vomiting, abdominal pain, and back pain as being dose and rate dependant, although the particular type of iron was not stated. While all intravenous iron products are associated with adverse events, the type of iron, dose and rate of infusion may be a major contributing factor (Madore, 2008). Administering a lower dose infusion at a slower rate may lead to fewer adverse reactions and consequently avoid the need to use a more costly iron product.

Health professionals have a responsibility to ensure that iron therapy is not only safe for patients but also that the therapy is cost effective considering the already high cost of managing anaemia. While a complete

Figure 5 Pre Dialysis TSAT level



cost analysis between the iron products is beyond the scope of this review, by simple comparison a cheaper iron product can be used safely and effectively by following a slower, lower dose iron polymaltose protocol.

Conclusion

From our retrospective study, iron polymaltose is safe and well tolerated by the majority of patients. There have been no anaphylactic or life threatening reactions and only a small number of patients (n= 7, 2.7%) experienced milder reactions such as nausea, vomiting, rash and urticaria which resolved quickly.

The results from our unit indicate that the current dosage of iron polymaltose is sufficient to maintain adequate iron storage parameters in the majority of patients.

A lower dose, slower rate iron polymaltose infusion may result in reduced adverse reactions and consequently switching therapy to an alternative more costly product. Using Iron polymaltose at the current rate and dose is effective and safe to use in CKD patients.

References

Aranesp® (darbepoetin alfa) Product Information Amgen 2008 available at http://www.aranesp.com/pdf/aranesp_pi.pdf

Besarab, A. Amin, N., Ahsan, M., Vogel, S., Zazuwa, G., Frinak, S., Zazra, J.J., Anandan, J.V., Gupta, A. (2000): Optimization of Epoetin Therapy with Intravenous Iron Therapy in Haemodialysis Patients. *J Am Soc Nephrology* 11, 520-538.

Chertow, G., Mason, P., Vaage-Nilsen, O., Ahlmen, J. (2004): On the Relative Safety of Parenteral Iron Formulations. *Nephrology Dialysis Transplantation* 19, 1571-1575.

Eprex® (epoetin alfa) Pre filled Syringes Consumer Medicine Information February 2008 Janssen Cilag, available at http://www.janssen-cilag.com.au/content/products/janssen-cilag.au_eng/pool_content/pdf/PI/Eprex_10208_PI.pdf

Horl, W. (2007): Iron Therapy for Renal Anaemia: How Much Needed, How Much Harmful. *Paediatric Nephrology* 22(4) 480-489.

Horl, W. (2007): Clinical Aspects of Iron Use in the Anaemia of Kidney Disease. *J Am Soc Nephrology* 18,382-393.

Johnson, D., Pollock, C., Macdougall, I. (2007): Erythropoiesis-Stimulating Agent Hyporesponsiveness. *Nephrology* 12, (4), 321-330.

Madore, F., White, C., Foley, R., Barrett, B., Moist, L., Klarenbach, S., Culleton, B., Tonelli, M., Manns, B. (2008):Clinical Practice Guidelines for assessment and management of iron deficiency. *Kidney International* 74 (S110),S7-S11

Macdougall, I. (2006): Experience with Intravenous Iron in Nephrology. *Seminars in Haematology* 08.004

McMahon, L. (2008): Caring for Australians with Renal Impairment Guidelines (CARI), Biochemical and Haematological Targets-Haemoglobin .*Nephrology* 13 (supp2) S44-S56

MIMS online www.mims.com.au, accessed August 2008

Mircescu, G., Garneata, L., Capusa, C., Ursea, N. (2006): Intravenous Iron Supplementation for the Treatment of Anaemia in Pre Dialysed Chronic Renal Failure Patients. *Nephrology Dialysis and Transplantation* 21(1) 120-124.

Newman, E., Ahmad, I., Thornton, A., Gibson, P .R. (2006): Safety of Iron Polymaltose Given as a Total Dose Iron Infusion. *Internal Medicine Journal* 36, 672-674.

Pollock, C., McMahon, L. (2005) CARI (Caring for Australians with Renal Impairment) Guidelines, Biochemical and Haematological Targets-Haemoglobin July 2005 available at http://www.cari.org.au/DIALYSIS_bht_published/Haemoglobin_rev_aug_2005.pdf

Roger, S. 2006 CARI (Caring for Australians with Renal Impairment) Guidelines, Biochemical and Haematological Targets-Iron April 2006 available at http://www.cari.org.au/DIALYSIS_bht_published/Iron.pdf

Saunders, J., Aravindan, A.N., Knaggee, D., Wong, J., Howlin, K.J., Clelend, B.G., Jefferys, A., Spicer, T., Suranyi, M.G. (2007):The Safety of Iron Polymaltose in Chronic Kidney Disease Patients. *Nephrology* 12, supplement 2, abstract 1176.

Silverberg, D., S., Iaina, A., Peer, G., Kaplan, E., Levi, B.A., Frank, N., Steinbruch, S., Blum, M. (1996): Intravenous Iron Supplementation for the Treatment of Anaemia of Moderate to Severe Chronic Renal failure Patients Not Receiving Dialysis. *American Journal Kidney Disease* 27 (2) 234-238.

Tagboto, S., Cropper, L., Turner, J., Bailey, G., Pugh-Clarke., K. (2008) Intravenous Iron in Chronic Kidney Disease: Haemoglobin change shortly after treatment of patients neither on dialysis nor on Erythropoietin. *Journal Renal Care* 34(3), 112-115.

Tonelli, M., Winkelmayer, W., Jindal, K., Owen, W., Manns, B. (2003) The cost effectiveness of maintaining higher hemoglobin targets with erythropoietin in hemodialysis patients. *Kidney International* 64, 295-304.

Yee, J., Basarab, A. (2002): Iron Sucrose: The Oldest Iron Therapy Becomes New. *American Journal of Kidney Disease* 40 (6) 1111-1121.

Zyl-Smit, R., Halkett, J. (2002): Experience with the use of an Iron Polymaltose (Dextrin) Complex Given by Single Total Dose Infusion to Stable Chronic Haemodialysis Patiens. *Nephron* 92, 316-323.