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Intravenous iron replacement

Management in general practice

Background
Iron deficiency is one of the most common nutritional deficiencies in Australia, and remains one of the most underdiagnosed conditions in general practice. The consequences of this condition can be subtle and the cause is often multifactorial.

Objective
The aim of this article is to review the safety of parenteral iron replacement therapy, and specifically intravenous infusion, in the general practice setting. The results of a recent clinical evaluation of 43 consecutive adult patients are reported.

Discussion
Intravenous iron polymaltose infusions are commonly used in the hospital setting with low rates of reported adverse reactions (including low rates of anaphylaxis and anaphylactoid reactions). In a primary care setting, patients were given low dose intravenous iron polymaltose as a slow injection diluted with normal saline, following a diagnosis of iron deficiency or iron depletion, with or without anaemia. Injections were given at intervals no more frequently than weekly. Serum ferritin levels were monitored following treatment, and as routine follow up. A total of 89 injections of intravenous iron were used in 43 patients. No serious adverse reactions occurred. The administration of low dose parenteral iron polymaltose in the primary care setting is well tolerated and is potentially a cost effective alternative to specialist care and hospital admissions.

Keywords: general practice; hematologic disease; iron deficiency, clinical evaluation

Iron deficiency is one of the most common nutritional deficiencies in Australia and remains one of the most underdiagnosed conditions in general practice.[1] It is estimated that about 8% of the premenopausal adult female population has biochemical iron deficiency, with less than one-quarter being anaemic.[1] The consequences of this condition can be subtle and the cause is often multifactorial.

The diagnosis of iron depletion can be made separately from any other condition,[1,2] such as anaemia, and the literature suggests that this diagnosis is made too infrequently, partially due to the methods of estimating what 'normal' should be.[3] Serum ferritin levels continue to be the most reliable diagnostic parameter.[2,4] Although its exact function is unknown, it most accurately reflects body iron stores. About 25% of iron deficient subjects have a serum ferritin in the range of 16–30 µg/L. Some argue that levels below 40–45 µg/L represent a state of iron shortage and should be actively treated.[3]

The treatment of iron deficiency can be difficult for a number of reasons: unacceptable risks, unacceptable side effects, or disadvantages of some preparations, compliance issues and the time taken to replace depleted stores.[5]

The consequences of iron depletion have been extensively described in the literature.[1,6–9] In summary:

- iron depletion is associated with alterations in many metabolic processes that may impact brain functioning. These include mitochondrial electron transport, neurotransmitter synthesis and degradation, protein synthesis and organogenesis
- there are consequences for altered foetal outcome and premature labour in pregnant women – maternal iron deficiency results in large placental size and small babies whose iron stores are insufficient to sustain them through rapid early growth
- bactericidal activity is decreased in most studies on iron deficient subjects
- cellular immunity is often altered in iron deficient humans
- iron deficiency anaemia limits maximal physical performance, submaximal endurance, and spontaneous activity.

Accumulated evidence provides ample justification for preventing and treating a common and easily correctable nutritional disorder.

Management of iron deficiency

Management of iron deficiency traditionally favours oral iron replacement as a first line approach. Patients are advised to increase their intake of red meat (haem iron) and/or use of oral iron formulations. Ferrous gluconate formulations seem to be better absorbed than the sulphate version; liquid oral iron formulations are also commonly used in general practice.[4] Simultaneous vitamin C ingestion enhances the absorption of nonhaem iron, as does the presence of haem iron.

However, oral replacement of iron has several well known disadvantages and side effects:

- gastrointestinal (eg. nausea, constipation or diarrhoea, abdominal pain and black stools [in up to 30% of patients])[10]
- compliance issues (5–30%)[10]
- poor absorption of nonhaem iron and very slow replacement of iron stores
- lack of relief of presenting complaint for a significant period of time (3–6 months in some cases).

Parenteral iron over oral replacement therapy?

If oral replacement therapy is ineffective or unacceptable, what alternative does the general practitioner have?

In Australia, traditionally intramuscular iron has been used, otherwise referral to a specialist undertaken: it is the authors' opinion that intramuscular iron is problematic. It is difficult to administer correctly; a 5–6 cm needle and a 'Z shape' approach is required, and there may be permanent scarring and staining.[11]

What about intravenous iron?

The product information recommends that this be used in certain situations only, including hospital settings. However, this conservative approach may no longer be necessary following changes to the formulation when iron dextran was superseded by iron polymaltose in 1992. The change in the formulation has significantly reduced adverse reactions to the administration of parenteral iron, especially anaphylaxis and anaphylactoid reactions.[12–16]

There is now a large body of experience demonstrating the safety and efficacy of total dose intravenous iron polymaltose infusions, especially with patients on dialysis,[15,16] in cardiology,[17–19] with inflammatory bowel disease[20,21] and in pregnancy.[22–24] Few published articles reported adverse reactions until recently with Haines et al,[25] who were the first to describe a series of gastroenterological patients with delayed onset adverse effects after total dose infusion of iron polymaltose, also stating however, that this is no reason not to continue to use this treatment.

Contraindications to parenteral polymaltose iron

- Hypersensitivity to iron hydroxide polymaltose complex
- Anaemia of causes other than iron deficiency
- Iron overload states (eg. haemochromatosis, haemosiderosis)
- Ostler-Rendu-Weber syndrome
- Chronic polyarthritis
- Severe bronchial asthma
- Severe inflammation or infection in kidneys or liver
- Uncontrolled hyperparathyroidism.

Evaluation

As part of a quality assurance project at a primary care clinic in Sydney (New South Wales), from April 2006 to December 2009, the outcomes of 43 consecutive adult patients who were administered low dose intravenous iron were monitored. Patients had a diagnosis of iron deficiency or iron depletion, with or without anaemia. Ferritin levels were 40 µg/L or less, and conventional (oral) treatment or intramuscular administration was either inadequate, inappropriate or unacceptable. Patients were made aware and understood the benefits and risks of treatment, including understanding that the administration of parenteral iron in the primary care setting is not endorsed by the Therapeutic Goods Administration.

Iron polymaltose 100 mg/2 mL was diluted in 0.9% normal saline (10–20 mL) and injected slowly over 5–10 minutes. Any immediate reactions were noted. The injections were given at intervals no more frequently than weekly. Patients were observed for 30 minutes after the first injection. In the unlikely event of anaphylaxis, appropriate resuscitation equipment was always available. Serum ferritin levels were monitored following treatment and at routine follow up 1–4 weeks later. Clinical review included enquiring about delayed adverse reactions.

Findings

A total of 89 injections of intravenous iron were given to 43 patients (*Table 1*). Serum ferritin levels rose by a mean of 18.1 µg/L (95% confidence interval [CI] 18.0–18.2) with each injection. No serious reactions were noted. One patient experienced 'flushing', by slowing the rate of infusion this reaction passed, and no further problems were encountered. One patient experienced a 'cold' sensation up the arm, and one a little retrosternal discomfort, again controlled by slowing the infusion rate. One patient noticed body aches the following day that settled spontaneously. We found that this method of iron replacement was generally well accepted by patients.

Discussion

This article is the first to describe the use of intravenous iron in the context of the general practice setting. Reported rates of anaphylaxis are rare, which was confirmed in this (albeit small) group. Haines et al[25] reported adverse reactions occurring in 13 of 50 consecutive gastroenterology patients. The reactions occurred up to 2 days after the total dose infusion and lasted 1–8 days. Symptoms were often multiple and included headache, nausea and/or vomiting, chills or fevers, arthralgia, faintness, rash and dizziness. Severe reactions, defined as being confined to bed or seeking medical attention, occurred in four patients. All reactions were transient with no lasting sequelae. Manoharan et al[26] responded to this paper stating their adverse reaction rates were much lower. They attributed this to premedication with antihistamines and corticosteroids.

In this sample of 43 patients there were only three minor adverse reactions. Patients received one-fifth of the total dose usually given by clinicians – none were premedicated. Patients were reviewed 1 and 4 weeks after the infusion. Recall bias may have reduced the incidence of reported adverse reactions in this study, especially minor reactions. However, it is unlikely that patients would forget being bedridden or needing to seek medical attention. As such, we

Table 1. Patient demographics and treatment summary

Patients	Cause of iron deficiency	Mean serum ferritin (µg/L) (95% CI)	Adverse reactions
• Total 43 – Female 40 – Male 3 • Median age 36 (age range 24–84 years)	• Reduced intake 6 • Increased loss 17 • Reduced absorption 6 • Oral not tolerated 3 • Unknown cause 15 (Note: Four patients had more than one cause of iron deficiency)	• Pretreatment 17.7 µg/L (17.6–17.8) • Post-treatment 97.9 µg/L (97.3–98.5) • Mean increase serum ferritin per 2 mL/100 mg polymaltose 18.14 µg/L (95% CI 18.03–18.24)	• Total number of doses 89 • Number of adverse reactions (all mild) 3

are confident that our reported rate of no severe adverse reactions is accurate, and in line with the majority of other reports.[27–29]

Summary

There is evidence from the literature that the safety of administering intravenous iron polymaltose has been unequivocally established. It would seem that the traditional methods of treating iron deficiency were dependant on the efficacy and safety of the products available at the time, perceptions which seem to persist.

With the advent of iron polymaltose with a record of safety and efficacy, there is more flexibility in choice in the management of iron depletion or deficiency for the treating physician and expectations of a better outcome for the patient.

Our experience with the product supports this view. General practitioners can safely use this method of low dose parenteral iron polymaltose in the primary care setting.

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