INTERNAL MEDICINE JOURNAL

Internal Medicine Journal **39** (2009) 252–255

BRIEF COMMUNICATION

Delayed adverse reactions to total-dose intravenous iron polymaltose

M. L. Haines[1,2] and P. R. Gibson[1,2]

[1]Department of Gastroenterology and Hepatology, Monash University, Melbourne, and [2]Department of Medicine, Box Hill Hospital, Melbourne, Victoria, Australia

Key words
iron deficiency, adverse effects, intravenous iron.

Correspondence
Peter Gibson, Department of Medicine, Box Hill Hospital, Box Hill, Victoria 3128, Australia.
Email: peter.gibson@med.monash.edu.au

Received 4 February 2008; accepted 12 July 2008.

doi:10.1111/j.1445-5994.2009.01898.x

Abstract

The rate of infusion reactions to total-dose intravenous iron polymaltose is very low, but the frequency and severity of adverse reactions following the infusion are unknown. In 50 consecutive patients, adverse reactions developed up to 2 days after the infusion in 26% and lasted 1–8 days (median 4). Severe systemic reactions occurred in 8%. Patients should be warned of the chance of delayed reactions and an alternative iron preparation should be considered if parenteral iron is again indicated.

Iron deficiency is a common clinical finding in gastroenterology patients, as a result of occult or overt gastrointestinal bleeding and/or impaired iron absorption secondary to coeliac disease or systemic inflammation. Iron is an essential element involved in oxygen transport and storage, growth, immune defence, energy metabolism and DNA synthesis. Chronic fatigue, frequently caused by anaemia, has a significant effect of the quality of life of patients with inflammatory bowel disease (IBD) and may debilitate patients as much as abdominal pain and diarrhoea.[1]

There are several strategies for iron repletion with both oral and parenteral routes of administration. Despite relative ease of administration, oral iron is limited by poor absorption, intolerance and induction of oxidative stress at the site of bowel inflammation.[2,3] Common gastrointestinal side-effects include nausea, bloating, diarrhoea, constipation and abdominal pain,[4,5] which may lead to poor compliance.

Funding: ML Haines was in receipt of a Pharmatel-Fresenius-Kabi Fellowship.
Potential conflicts of interest: PR Gibson has consulted for Aspen Pharmacare Pty Ltd.

Intravenous iron replacement therapy can be used to replenish iron stores in iron deficient patients with or without coexisting anaemia. Parenteral iron obviates the need for absorption, can be given in large doses and it may reduce inflammation through inhibition interferon-γ activity and reduction of circulating levels of tumour necrosis factor-α and peroxides.[6] The types of parenteral iron preparations available vary across the world, but, in Australia, only iron polymaltose and iron sucrose are available, the latter being used in the event of intolerance to iron polymaltose.

Iron polymaltose is very similar to iron dextran in terms of stability and structure, but is rarely associated with the problem of anaphylaxis that led to the withdrawal of iron dextran from the market. A major advantage of iron polymaltose is that it can be administered at high single doses (total-dose therapy). Administration requires long infusion times of up to 4–5 h, but adverse reactions associated with the infusion itself are very uncommon, occurring in 3.6% and necessitating cessation of the infusion in less than one in 60.[7] Furthermore, there is no apparent need for premedication with corticosteroids and antihistamines as was routine with the use of iron dextran.

Product information on iron polymaltose describes possible adverse effects of its use, but states that they are reported infrequently. Anecdotal experience suggests

Table 1 Adverse reactions reported in the 8 days following a total-dose iron polymaltose infusion

Adverse reaction	*n* (% reactions)	Severity		
		Mild	Moderate	Severe
Headache	10 (31)	3	4	3
Nausea and/or vomiting	7 (22)	2	3	2
Chills and fevers	6 (19)	2	2	2
Arthralgia	4 (13)	2	1	1
Faintness	2 (6)	2	0	0
Rash	2 (6)	2	0	0
Dizziness	1 (3)	1	0	0
Total	32	14 (44%)	10 (31%)	8 (25%)

that, delayed systemic reactions, such as headaches, dizziness, syncope, arthralgia, chills, fever and myalgia, may occur, but their frequency and severity of such reactions have not been determined.

The aim of this study was to evaluate prospectively the post-infusion safety and tolerability of intravenous iron polymaltose administered as a total-dose infusion in gastroenterology patients with iron deficiency.

Consecutive gastroenterology patients who received iron polymaltose as a total-dose infusion in the period from March 2007 to February 2008 were included in this prospective audit. Medical records were reviewed and patient characteristics recorded including age, sex, cause of iron deficiency, concomitant medications and dose of iron polymaltose administered. Previous adverse reactions to iron polymaltose were noted. Laboratory values pre-infusion were recorded: haemoglobin, mean cell volume, platelets, iron, transferrin, transferrin saturation, ferritin and C-reactive protein.

The treating physician (M. L. H.) contacted all patients by telephone 8 days following the iron infusion and enquired about adverse events, including time of onset after the infusion, duration and severity. Severity was graded as mild, moderate and severe according to the following criteria: (i) mild reactions resulted in no limitation of daily activities, (ii) moderate reactions caused limitation of daily activities, including ability to work, and (iii) severe reactions were those in which patients were confined to bed and/or medical attention sought.

Fifty patients received iron polymaltose as a total-dose infusion during the study period. The dose administered was weight-based and no pre-medications were used. The median age was 43 years (range 18–87) and 60% were women. Iron deficiency was confirmed biochemically in all patients and was due to Crohn's disease in 21 (42%), ulcerative colitis in 8 (16%), coeliac disease in 3 (6%), gastric ulceration in 4 (8%) and a gastric angiodysplasia in 1 (2%). The cause of iron deficiency was yet to be determined in 13 (26%).

There were two minor infusion-related reactions, neither requiring discontinuation of the infusion. There was a total of 32 adverse reactions by 13/50 (26%) patients during the week following intravenous iron polymaltose and these are shown in Table 1. Eight reactions (25%) were classified as severe, 10 (31%) moderate and 14 (44%) mild. Six adverse events started 2 days and 12 started 1 day after the infusion, while 12 started on the same day of the infusion. The median duration of adverse events was 4 days (range 1–8) and all reactions completely resolved.

Baseline characteristics and laboratory values of those who did and did not have an adverse reaction are shown in Table 2. A significantly higher number of patients who had a reaction were female (85%). The dose of iron received and previous iron infusion had no impact on the rate of adverse events. Previous experience of iron polymaltose infusion was not necessarily predictive of the presence or absence of adverse reactions as shown in Table 2. Current steroid use offered little protection against the development of side-effects.

Table 2 Comparison of demographics and laboratory values between patients who did and did not report an adverse reaction to total-dose iron polymaltose infusion

	No reaction	Reaction
Number of patients (%)	37 (74)	13 (26)
Male (%)	18 (49)	2 (15)*
Mean age (range), years	49 (23–87)	36 (18–70)
Mean dose iron polymaltose (range), g	1.6 (1–2)	1.6 (0.8–2)
Previous iron polymaltose (%)	12 (32)	5 (38)
Without reaction	11	3
With reaction	1	2
Current prednisolone use (%)	9 (24)	2 (15)
Mean haemoglobin (g/L)	120	123
Mean platelet count	316×10^9/L	359×10^9/L
C-reactive protein > 5 mg/L (%)	11 (30)	2 (15)

*$P = 0.034$ compared with no reaction (Fisher's exact test).

Four patients (8%) had severe adverse reactions following parenteral iron. Patient 1 was an 18-year-old woman with coeliac disease who had not had a previous infusion. She developed a headache, nausea and vomiting and fevers 2 days after her iron infusion, which persisted for 5 days. She saw her general practitioner and was unable to attend university. Patient 2 was a 36-year-old woman with iron deficiency of unknown cause. The day of her iron infusion she developed a headache, chills, arthralgia, faintness and a slight rash. She was confined to bed for 8 days. Patient 3 was a 48-year-old woman with Crohn's disease who had had several iron polymaltose infusions in the past with no previous adverse reaction. Two days after the infusion she developed a headache, nausea, vomiting, faintness, dizziness and a rash, which persisted for 1 week. She contacted the hospital several times during that week and saw her general practitioner. She was confined to bed for 3 days. She has subsequently had two infusions with iron sucrose without side-effects. Similarly, patient 4 was a 19-year-old man with Crohn's disease who had no reaction to previous parenteral iron. Shortly after his infusion, he developed a severe headache and arthralgia, which lasted 1 day only. He was kept an extra several hours in hospital for observation because of these reactions.

Total-dose intravenous iron polymaltose is used widely throughout Australia, and locally the rate of infusion reactions is low.[7] This is the first series to document the incidence of post-infusion reactions, which was high at 26%. Four patients (8%) had severe reactions, which resulted in incapacity and/or the need to seek medical attention. Many of the reactions started as late as 2 days after the iron infusion and lasted up to 8 days.

The nature and timing of the symptoms experienced indicated that they were likely to be caused by the infusion and not be associated with the underlying or intercurrent illness. Over half of the patients had IBD, which potentially might make the patients more susceptible to systemic inflammatory reactions from the intravenous iron, but the rate of adverse effects was similar in patients with non-inflammatory disease. The relatively small number of patients audited might also lead to error in the frequency of adverse events, but it was a 1-year experience and the frequency of events was sufficiently high to raise concern.

There are four implications of these findings:

1. In advising the use of parenteral iron, patients should be warned of the possibility of transient adverse events in the week after the infusion and they should be encouraged to report them to the attending clinician.
2. Previous uneventful iron infusions do not guarantee freedom from adverse effects on subsequent infusions.
3. Alternative sources of parenteral iron should be considered if iron deficiency recurs. Iron sucrose has an excellent safety record and post-marketing surveillance safety reports show that it is the safest parenteral iron complex available.[8] However, total-dose infusions are not possible as only up to 300 mg or 7 mg/kg are considered safe and tolerable.[9,10] In patients with IBD-associated anaemia more than 1000 infusions have been given in trials without major side-effects.[11–13]
4. This unexpected frequency of adverse events should not deter clinicians from the use of intravenous iron, as the problems associated with oral iron replacement therapy, including poor compliance, high rate of side-effects and slow and inadequate iron repletion, far outweigh the chance of transient, albeit occasionally severe adverse effects from a therapy that ensures iron repletion.

References

1 Gasche C. Anemia in IBD: the overlooked villain. *Inflamm Bowel Dis* 2000; **6**: 142–50. Discussion 151.
2 Oldenburg B, van Berge Henegouwen GP, Rennick D, Van Asbeck BS, Koningsberger JC. Iron supplementation affects the production of pro-inflammatory cytokines in IL-10 deficient mice. *Eur J Clin Invest* 2000; **30**: 505–10.
3 Erichsen K, Hausken T, Ulvik RJ, Svardal A, Berstad A, Berge RK. Ferrous fumarate deteriorated plasma antioxidant status in patients with Crohn disease. *Scand J Gastroenterol* 2003; **38**: 543–8.
4 Millar AD, Rampton DS, Blake DR. Effects of iron and iron chelation in vitro on mucosal oxidant activity in ulcerative colitis. *Aliment Pharmacol Ther* 2000; **14**: 1163–8.
5 Babbs CF. Oxygen radicals in ulcerative colitis. *Free Radic Biol Med* 1992; **13**: 169–81.
6 Weiss G, Meusburger E, Radacher G, Garimorth K, Neyer U, Mayer G. Effect of iron treatment on circulating cytokine levels in ESRD patients receiving recombinant human erythropoietin. *Kidney Int* 2003; **64**: 572–8.
7 Newnham E, Ahmad I, Thornton A, Gibson PR. Safety of iron polymaltose given as a total dose iron infusion. *Intern Med J* 2006; **36**: 672–4.
8 Bailie GR, Lane PL, Clark JA, Stang PE, Lane CE. Safety surveillance of intravenous iron preparations – relative rates of hypersensitivity reactions reported in the USA. *J Am Soc Nephrol* 2003; **14**: 458A.
9 Chandler G, Harchowal J, Macdougall IC. Intravenous iron sucrose: establishing a safe dose. *Am J Kidney Dis* 2001; **38**: 988–91.
10 Schroder O, Schrott M, Blumenstein I, Jahnel J, Dignass AU, Stein J. A study for the evaluation of safety and tolerability of intravenous high-dose iron sucrose in patients with iron deficiency anemia due to gastrointestinal bleeding. *Z Gastroenterol* 2004; **42**: 663–7.

11 Gasche C, Dejaco C, Waldhoer T, Tillinger W, Reinisch W, Fueger GF *et al.* Intravenous iron and erythropoietin for anemia associated with Crohn disease. A randomized, controlled trial. *Ann Intern Med* 1997; **126**: 782–7.
12 Gasche C, Dejaco C, Reinisch W, Tillinger W, Waldhoer T, Fueger GF *et al.* Sequential treatment of anemia in ulcerative colitis with intravenous iron and erythropoietin. *Digestion* 1999; **60**: 262–7.
13 Gasche C, Waldhoer T, Feichtenschlager T, Male C, Mayer A, Mittermaier C *et al.* Prediction of response to iron sucrose in inflammatory bowel disease-associated anemia. *Am J Gastroenterol* 2001; **96**: 2382–7.