Internal Medicine Journal **36** (2006) 672–674

BRIEF COMMUNICATION

Safety of iron polymaltose given as a total dose iron infusion

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Key words
safety, anaphylaxis, total dose iron infusion, iron deficiency, premedication

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Received 7 December 2005; accepted 12 February 2006.

doi:10.1111/j.1445-5994.2006.01156.x

Abstract

An audit of the in-hospital safety and tolerability of 401 infusions of iron polymaltose in 386 patients has shown no cases of anaphylaxis or other cardiorespiratory compromise. The infusion was terminated prematurely because of adverse events in six patients (1.6%). No adverse events occurred within the first 15 min of the infusion. Premedication (in 24%) was not associated with fewer adverse events. Fear of anaphylaxis should not inhibit the use of total dose iron infusion and the practices of premedication and of medical supervision during the first 15 min of the infusion should be abandoned.

Iron deficiency is a common finding among hospitalized patients. Efficient iron replacement can result in improved cardiac function, reduced length of stay in the hospital and improved quality of life in those with congestive heart failure[1,2] whereas oral iron replacement in deficient adolescents has resulted in improved cognitive function.[3] Iron deficiency is both underrecognized[4] and undertreated in patients in hospitals.[5]

Current published guidelines regarding iron repletion strategies favour oral iron in all patients unless 'there is an intolerance to at least two oral preparations or non-compliance'.[6] However, the use of oral iron, although easy and convenient, is limited by such factors as absorption and side-effects (experienced in up to 40% of patients), which lead to poor adherence.[7–9] Oral iron supplementation has been shown to be ineffectual in patients with chronic kidney disease[10] whereas the cytokine milieu in chronic inflammatory conditions results in poor iron absorption through mechanisms mediated by interleukin-6 and hepcidin.[11]

Parenteral iron therapy enables a large dose to be given and obviates the need for absorption. This is particularly important in circumstances where there are ongoing gastrointestinal losses and/or there is an impaired absorption, such as in inflammatory bowel disease.[12] The reluctance to recommend parenteral iron as a primary therapy appears to stem at least partly from concerns regarding its safety. Iron polymaltose delivered i.m. is not a preferred option because it requires a deep injection using 'Z technique' to avoid skin pigmentation, resultant disfigurement and subsequent medicolegal claims[13] and may be complicated by sterile abscesses, pain or even sarcoma[14] at the injection site. Furthermore, at 100 mg per 2 mL injection, repeated injections are usually required to reach target iron repletion.

Intravenous iron does not share these local complications and, in some forms, can be given as a total dose infusion where iron stores can be repleted in a single treatment episode. Apart from the greater cost of such a therapy over oral iron, concerns are mainly about its safety, particularly anaphylaxis or anaphylactoid reactions. These reactions are reported to be more common in patients receiving therapy with angiotensin-converting enzyme (ACE) inhibitors.[15] Because of the perceived dangers, direct supervision during the first 15 min of the infusion is recommended. In addition, a premedication of a corticosteroid with or without an antihistamine is often used, but this practice is not based on published evidence.

The aims of the present study were to evaluate the safety and tolerability of iron polymaltose given as a total dose

Funding: I. Ahmad was in receipt of a Pfizer-Altana Gastroenterology Fellowship.
Potential conflicts of interest: P. R. Gibson has participated in one Advisory Board meeting for Baxter Healthcare/Vifor in 2002.

iron infusion across three Melbourne teaching hospitals and to examine the need for premedication and intensive medical monitoring.

The medical records of 401 patients having total dose iron infusions with iron polymaltose undertaken at three Melbourne teaching hospitals over the same 2-year period (from August 2002 to August 2004) were reviewed. The indication, tolerance, safety and dosage of i.v. iron were examined in the records. The indication for each infusion was recorded. To provide an insight into the patient characteristics and the potential influence of concomitant medication, the referring unit and details of current medications were also recorded in the Box Hill Hospital cohort. The type and dosage of premedication (if used) were also recorded. Any reaction noted in the patient's observation chart during or after the infusion while the patient remained at the hospital was defined as an adverse reaction. The study was carried out according to the National Health and Medical Research Council guidelines for clinical audit. Proportions were examined by χ^2 analysis (Microstat 4.1; Ecosoft, Indianapolis, IN, USA, 1984). A *P*-value less of 0.05 or less was considered significant.

The protocol used for the administration of iron polymaltose was similar across the three hospitals, except for the use of premedication. At the Maroondah and Frankston hospitals, premedication was routinely used, whereas it was applied at Box Hill Hospital only if requested by the attending physician. For each infusion, the dose was calculated from standardized charts using the patient's weight and haemoglobin and infused as per hospital protocol.[16] The infusion of iron polymaltose (Baxter Healthcare, Sydney, Australia, or Sigma Pharmaceuticals, Melbourne, Australia) was given in 500 mL 150 mmol/L NaCl, and started at 40 mL/h under the direct supervision of a medical practitioner for the first 15 min. If no adverse reactions were noted, the infusion rate was increased to 120 mL/h after 50 mL had been given and further supervision was provided by nursing staff. The patient was observed for 1 h after completion of the infusion.

In all, 401 infusions were examined in 386 patients. The median age was 74 years (range, 17–96 years) and 60% were women. The mean dosage given was 1338 mg (range, 800–2350 mg). Iron deficiency had been biochemically proven in all patients in the setting of known blood loss in 181 (45%), anaemia where the cause had yet to be definitively determined in 92 (23%), inflammatory bowel disease in 56 (14%), chronic kidney disease in 40 (10%) of whom none was receiving dialysis, coeliac disease in 16 (4%) and cancer in 16 (4%). At Box Hill Hospital, 46% of infusions were initiated by the Gastroenterology Unit, 26% by the General Medicine unit, 15% by the Renal Medicine unit, 10% by the Oncology/Haematology unit with the remaining 3% shared by several units. The use of i.v. iron varied markedly across hospitals with 27 infusions at Frankston Hospital, 77 at Maroondah Hospital and 297 at Box Hill Hospital over the same 2-year period.

Adverse reactions were noted in 22 (5.7%) patients. These are listed in Table 1. No patient receiving more than one infusion experienced an adverse reaction. In six (1.6%) patients, the reaction was significant enough to warrant cessation of the infusion. The most common adverse reaction was a rash (usually urticarial in nature). The most serious adverse reaction was a seizure in a patient with known epilepsy. No cases of anaphylaxis or anaphylactoid reactions were recorded. None of the adverse reactions observed occurred in the first 15 min of infusion. Interestingly, three patients with an urticarial rash went on to complete an otherwise uneventful infusion.

In 294 (77%) patients, no premedication was used. Of the 92 infusions where premedication was given, three received hydrocortisone (100 mg) alone and 89 a combination of hydrocortisone and promethazine (20 mg). Adverse events occurred in 6 (6.5%) patients who received premedication, compared with of 16 (5.4%) patients who did not ($P = 0.45$).

Table 1 Adverse events and the need to cease the infusion of iron polymaltose according to the use of premedication or not

Reaction	All infusions (*n* = 386)		With premedication (*n* = 92)		Without premedication (*n* = 294)	
	No. patients	Infusion ceased	No. patients	Infusion ceased	No. patients	Infusion ceased
Rash	6	3	2	—	4	3
Nausea/light-headedness	5	1	2	—	3	1
Chest pain	3	1	—	—	3	1
Cannula site reaction	2	—	—	—	2	—
Fever	2	—	1	—	1	—
Myalgia	2	—	—	—	2	—
Seizure	1	1	1	1	—	—
Headache	1	—	—	—	1	—
Total	22	6	6	1	16	5

n is the number of patients. No adverse events occurred in seven patients who received more than one infusion.

Of the 294 patients in whom medication charts were reviewed, 42 (14.3%) were receiving therapy with ACE inhibitors or angiotensin II receptor antagonists. None of these patients experienced an adverse reaction to i.v. iron.

Fear of anaphylaxis or anaphylactoid reactions has been a significant factor against learned advice regarding treatment choices in repleting iron stores. In clinical practice, such fears have probably also limited the use of i.v. iron in the management of iron deficiency. The marked heterogeneity in the use of i.v. iron within the same 2-year period across the three hospitals in the one city may have at least partly reflected this fear.

Much of the published work regarding anaphylaxis centres on experience with iron dextran with rates of anaphylaxis reported to be as high as 0.6% with adverse reactions seen in up to 26%.[17,18] These reactions are thought to be mediated by a preformed Immunoglobulin E antibody to the dextran moiety. Because of these reactions and unacceptable fatalities, iron dextran was withdrawn from the market.

The experience of the present study indicates that total dose infusion of iron polymaltose is a well-tolerated and safe means of repleting iron. The incidence of adverse reactions is small (3.6%), much lower than the reported incidence with iron dextran. Most of the reactions seen were minor and resulted in cessation of the infusion in less than one in 60 infusions. The taking in of ACE inhibitors did not identify an at-risk group, although the numbers were small. The delayed effects of iron infusions sometimes seen (such as myalgias and headaches) were not examined as the primary aim was to assess the immediate safety and tolerability. Although the number of infusions reviewed in our audit is modest and may not detect a small incidence of anaphylaxis, we have continued to use i.v. iron polymaltose because of the completion of our formal study without the occurrence of any serious adverse events in 140 infusions.

Infusion protocols demand that medical staff be in attendance for the initial period (usually 15 min) of the infusion. This is based on the need for rapid institution of emergency therapy if anaphylaxis occurs. In the setting of a busy general hospital, such a practice is impractical, inconvenient and a potential source of treatment delay and frustration while the day procedure staff wait for the doctor to arrive. The findings of the present study argue that such a practice is no longer necessary. Furthermore, the use of premedication is also part of routine protocols in many centres. There can be no justification for continuing this unnecessary practice.

In conclusion, treatment of iron deficiency with a total dose infusion of iron polymaltose is a safe and well-tolerated means of iron repletion. Fear of anaphylaxis should no longer limit its use. There would appear to be no justification for the use of premedication when giving iron polymaltose i.v. and the practice of intense medical monitoring over the first 15 min of the infusion should be abandoned.

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