Safety of RAPid INJECTion of Undiluted Ferric Carboxymaltose to Patients with Iron Deficiency Anaemia (RAPINJECT): A Phase II Single Arm study

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Keywords

Anaemia, Iron Deficiency, Administration and Dosage

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Abstract

Background

Ferric carboxymaltose is increasingly utilised to treat iron deficiency and is usually diluted in saline and administered as an intravenous infusion over 15 minutes. Whilst this is highly convenient compared with older formulations, we hypothesised the drug could be administered safely given as a rapid bolus injection.

Aims:

To define the risk of serious adverse events following administration of an undiluted, rapid, high dose ferric carboxymaltose injection. Secondary aims included all other adverse events, as well as longitudinal effects on haemoglobin, iron stores, phosphate, and hepcidin.

Methods:

In a single arm, Phase II study in 121 patients with iron deficiency anaemia, we administered up to 1000mg of ferric carboxymaltose as a rapid undiluted bolus injection, and recorded adverse events and collected blood samples over the first hour, and again at two and four weeks post-treatment.

Results:

No patient experienced a serious adverse event. Flushing during the injection was common, as was a transient headache in the subsequent weeks. A single patient experienced Grade 3 chest tightness necessitating emergency department assessment but not admission or treatment. Treatment produced an average 12.3g/L improvement in haemoglobin within two weeks, but commonly caused reductions in serum phosphate (although none of these were

clinically symptomatic). Parenteral iron caused elevations in hepcidin sustained to four weeks post injection. Patients stated they would be prepared to receive the treatment again.

Conclusion: Rapid injection of undiluted ferric carboxymaltose is well tolerated and could provide an approach to treat patients in the ambulatory setting.

Introduction

Iron deficiency is a common clinical problem, for example affecting over 10% of pre-menopausal women in the US and Australia.[1, 2] Although oral iron treatment is often adequate, it is complicated by gastrointestinal adverse effects which may limit its acceptability.[3] Intravenous iron is indicated in patients intolerant to oral iron or in whom oral iron has been ineffective, and restores iron stores and raises haemoglobin more rapidly than

oral therapy.[4-7] Ferric carboxymaltose (FCM), along with Iron isomaltoside and Ferumoxytol, is one of the new generation iron-carbohydrate formulations that can provide total dose iron replacement over 1-2 infusions. FCM has been approved for intravenous administration of up to 1000mg of iron in a single infusion, diluted in up to 250mL saline and given over 15 minutes.[8] Compared with older generation intravenous iron formulations, administration of FCM is safe and rapid, and can be given in the ambulatory and even primary care setting[9, 10] as long as the infrastructure and personnel to cope with a serious allergic or anaphylactic reaction are available. FCM is widely used in the treatment of iron deficiency anaemia and restitution of iron stores in patients with complex conditions such as inflammatory bowel disease [11], recurrent bleeding[12], heart failure [13], and renal disease [14]; it is also emerging as a therapeutic option in patients with less complex iron deficiency, for example in iron deficient fatigued women [15], and in the antenatal [16] and post-partum setting [17]. Parenteral iron may cause upregulation of the master regulator of systemic iron homeostasis, hepcidin, although longitudinal effects require further characterisation. Upregulation of this hormone may prevent absorption of oral iron, which would have direct implications for clinical advice to patients post-administration of parenteral iron.

Doses of up to 200mg FCM have been approved for rapid bolus administration, and higher doses may be given as a slow injection over 15 minutes [18], which may be impractical. However, more rapid bolus injection of higher doses of FCM could simplify administration of total dose iron replacement without the ancillary requirements of preparing an infusion, especially in outpatient settings outside hospitals (for example, in primary care). To test the safety of this approach, we undertook a Phase II single arm trial of rapid injection of up to 1000mg of undiluted FCM in patients with iron deficiency anaemia. The primary outcome of this study was the incidence of serious adverse events related to the FCM injection. We also

sought to confirm effects of FCM injection on milder adverse events. Finally, we sought to assess longitudinal effects of parenteral iron treatment on haemoglobin, iron stores, phosphate (which has been observed to be reduced in patients receiving FCM), and hepcidin.

Methods

We undertook a single centre, single arm, Phase 2 safety study. In an initial Stage, the dose of undiluted FCM administered as a bolus was escalated from 500mg (3 patients) to 800mg (3 patients) and finally to 1000mg (6 patients); dose escalation was only performed if no serious (Grade 4 or 5) adverse events were observed. Patients in this stage requiring further doses of iron (up to a total of 1000mg) were administered the balance of the dose at the completion of the study period. In the next Stage, up to 1000mg FCM (based on calculated iron deficit, maximum dose of 20mg/kg) was administered to patients as an undiluted bolus (100 patients). The primary outcome of the trial was the incidence of Serious Adverse Events (SAEs) defined as adverse events resulting in death, or were life threatening (i.e. the subject was at risk of death at the time of the event), required inpatient hospitalisation, resulted in persistent or significant disability or incapacity, or an important medical event (i.e. although not immediately life threatening, required intervention to prevent a more serious outcome from occurring). We hypothesised that there would be no SAEs from this approach. The primary outcome was incidence of SAEs within 1 hour, as we hypothesised events due to rapid injection of IV iron would occur early; secondary outcomes were incidence of SAEs at 24 hours, 2 weeks and 4 weeks, as well as changes in haemoglobin and ferritin concentrations.

Patients

We recruited patients aged 18 years or older referred for intravenous iron infusions for iron deficiency anaemia (defined as haemoglobin<120g/L in women, <130g/L in men; and either ferritin<30micro/L or transferrin saturation<20%) to the haematology service at Monash Health, Melbourne Australia. As a tertiary referral centre, all patients had been referred for further specialist treatment from their primary care physician. Patients were excluded (Stage 2 or 3) if they were pregnant, presently an inpatient unlikely to be discharged from hospital with the next two weeks, had severe anaemia judged to require transfusion or with haemoglobin <60g/L, had ongoing blood loss requiring surgical or endoscopic intervention within the next 7 days, had anaemia due to non-iron deficiency causes, had end stage renal failure requiring erythropoietin therapy, had another acute or chronic medical condition that the investigators considered made them an unsuitable candidate for enrolment in the study or for which they were not expected to survive beyond 3 months, had known hypersensitivity or history of adverse reactions to iron formulations, a recent history (<4 weeks) of atopy, had a history of hereditary or transfusion related iron overload, had elevated liver transaminases (>twice the upper limit normal), had a history of chronic abuse of analgesics, alcohol, tranquilizers, or opioids, were dependent on alcohol or illicit drugs, or had received a blood transfusion in the previous 2 weeks or iron infusion within the past 4 weeks. No patient had received FCM previously. All patients in Stage 3 of the study received 1000mg FCM.

Study procedures

Following consent intravenous cannulas were sited and flushed to checked for extravasation. Baseline bloods for haemoglobin, and iron biochemistry were collected. The study protocol specifically avoided the use of routine premedications (e.g. hydrocortisone). Participants in Stage 3 received 1000mg FCM; 20mL of undiluted FCM was administered as a push injection over at least ten and up to sixty seconds. Adverse events were passively elicited by

asking the open question: “have you noticed any problems?” at one hour, by telephone 24 hours, and in person at two and four week visits post administration. We graded adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE).[19] Patients requiring more than 1000mg iron replacement (calculated according to the Ganzoni formula) were given the residual dose as a second infusion after the four week follow up period using standard infusion protocols.

Sample size

The study was designed to be able to determine a Grade 4-5 serious adverse event rate of 0% with an upper 95% confidence limit of 3%; incorporating an expected 12% loss to follow up, a sample size of 112 was needed.

Laboratory measures

Haemoglobin (Unicel DxH cell lyse, unicelDxH800, California USA), ferritin (Beckman Coulter, Brea, USA performed on the Beckman Coulter Dxi800 USA) and transferrin saturation (Beckman Coulter Clare, Ireland performed on the Beckman Coulter AU5800, Japan) were measured at baseline, and after 2 and 4 weeks. To measure the kinetics of hepcidin elevations following administration of parenteral iron, in a subset of ten individuals we also measured serum hepcidin (DRG Hepcidin 25 HS ELISA, DRG GMBH, Germany) at baseline, immediately after infusion, and at 2 and 4 weeks.

Ethics

The trial was approved by the Monash Health Ethics Committee, and was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12612000653864).

Results

Between February 2014 and November 2016, we recruited 12 participants to the initial stage and 109 participants to the second stage of the trial; an additional 9 participants were recruited to ensure sufficient samples were available for hepcidin analysis. The mean age was 45.7 years [range 18 to 86 years]. There were 104 females, of whom 61 were aged 45 years or under. Mean weight was 79.7 kg [range 44.2 to 182 kg].

Serious Adverse Events

There were no serious (Grade 4 or Grade 5) adverse events reported either immediately following infusion or during the course of the trial (0/121, 0.0% [0.0-2.5%]). There was a single case in which the full dose of drug could not be completed due to an adverse event. In this case, during infusion, a patient developed profound anxiety and reported chest pain. The infusion was ceased and the patient transferred to the hospital emergency department for clinical assessment: symptoms resolved spontaneously, the ECG was unchanged, there was no elevation in cardiac enzymes, and the patient was discharged home within four hours. We adjudicated this occurrence as a Grade 3 adverse event.

Adverse events

As shown in Table 1, within one hour of infusion, there were 70 adverse events reported in 66 individuals; the most common being a sensation of facial flushing (55 patients). Three patients reported transient arm pain that resolved following drug administration. Between one and 24 hours, there were another 33 adverse events in 29 patients (the most common being headache, reported by 14 patients). At 2 weeks post-infusion, a further 45 adverse events in 37 patients were reported, the most common being headache (10 patients) and myalgias (5

patients). By 4 weeks post-infusion, a further 14 adverse events had been reported in 14 patients.

On average, there was no decline in baseline and post-infusion systolic (P=0.6733) or diastolic (P=0.4981) blood pressure. A single patient experienced a greater than 40mmHg decline in systolic blood pressure following the infusion, from 180/115 to 120/76; this had increased to 189/90 by 15 minutes post infusion. The patient was 80 years of age, and interestingly did not report any subjective adverse events. The maximum post-infusion increase in blood pressure was from 117/85 to 150/87.

Efficacy

As shown in Figure 1, there was a significant rise in haemoglobin concentration from baseline (mean g/L [SD]: 102.1 [99.8, 104.3], n=121) to two weeks post infusion (114.4 [112.5, 116.3], n=116, P<0.0001 for change from baseline) to four weeks post infusion (120.3 [118.2,122.3], n=112, P<0.0001 for change from baseline), P<0.0001 for difference in mean between each timepoint. Ferritin concentrations rose rapidly from baseline (geometric mean 7.1 ng/mL [6.3, 8.1], n=121) to two weeks post infusion (266.9 ng/mL [238.7, 298.4], n=117, P<0.0001 for change from baseline) but declined to a still elevated level by four weeks (113.5 ng/mL [99.1, 130.0], n=113, P<0.0001 for change from baseline). Transferrin saturation increased from baseline (geometric mean 6.3% [5.4, 7.2], n=120) to 2 weeks (22.3% [20.6, 24.2], n=113, P<0.0001 for change from baseline) and declined slightly by 4 weeks (20.3% [18.7, 22.0], n=111, P=0.019 for change from 2 weeks).

Finally, in a subset of 10 patients, we observed that there was no change in hepcidin from baseline (geometric mean 2.5ng/mL [1.5, 4.2]) to immediately post-infusion (2.4 [1.2, 4.4]).

However, after two weeks, hepcidin levels had significantly increased (18.9 [13.1, 27.3]) and did not change after a further 2 weeks (18.2 [11.3, 29.4]).

Hypophosphataemia

There were no instances of clinically symptomatic hypophosphataemia. However, serum phosphate fell from a mean of 1.14 mmol/L at baseline (n=92) to 0.70 mmol/L after 2 weeks (n=115), before increasing to 0.88 mmol/L by 4 weeks (n=90); P<0.0001 for difference in mean between each timepoint (Figure 1); phosphate levels were still a mean 0.24 mmol/L lower at 4 weeks compared with baseline (P<0.01, paired t-test). A phosphate <0.6 mmol/L was not observed in any participants at baseline, but at 2 weeks was seen in 37/115 (32.2%), and at 4 weeks was observed in 11/90 (12.2%).

Exploratory analyses indicated no evidence of a difference in serum phosphate at 2 weeks between individuals with symptomatic adverse events (Grade 1, mean phosphate 0.74 mmol/L, N=35; Grade 2, mean phosphate 0.71 mmol/L, N=2) and those not reporting an adverse event (mean phosphate 0.71 mmol/L, N=77).

Patient Acceptability

Eighty six participants answered questions about acceptability of the rapid infusion regimen (this 'yes/no' question was introduced during the study and some early participants were not asked). Eighty five of those responding were satisfied with their treatment approach, and also responded that they would be prepared to receive the drug again.

Discussion

Ferric carboxymaltose is one of several new generation intravenous iron formulations that enable rapid restitution of iron stores in the outpatient setting. We have studied whether FCM can be safely administered as an undiluted, rapid bolus to patients with iron deficiency anaemia. Our data indicate that this regimen did not cause serious adverse events. However, the regimen was associated with a high incidence of patient-reported transient flushing symptoms, which did not limit administration. Our data also provide a time course of haemoglobin, iron stores and hepcidin elevation in response to FCM, and demonstrate the rapid and frequent onset of biochemical hypophosphataemia induced by the drug.

High (i.e. 500mg-1000mg) doses of FCM are currently usually diluted in saline and administered in an intravenous infusion over 15 minutes. Current Australian product information recommends that doses of up to 1000mg can be given undiluted, but should be administered over 15 minutes;[18] this approach is inconvenient as it requires a syringe driver or health care worker to provide the infusion over this duration. In our study, we were able to safely inject the complete dose of up to 1000mg over at least 10 and up to 30 seconds. The main adverse event observed with this regimen was flushing, which has been previously described as a common adverse drug reaction affecting 1-3.6% of patients receiving FCM;[20] our rapid method of administration was associated with a particularly high rate (~50% of patients) that is likely higher than that seen in current infusion protocols. This reaction was self limiting, was classed as Grade 1 in 95% of cases, and did not discourage participants from being willing to accept this regimen of administration again in the future; nevertheless, in routine clinical practice, the very high incidence of this adverse event may limit tolerability of this approach and the willingness of clinicians to provide it in ambulatory settings. Flushing may have been caused by release of labile iron from the drug but this would require confirmatory testing in future studies.[9] Beyond this effect, we did not observe clinical adverse

reactions out of proportion with those presented in previous reports. We observed a higher risk of delayed headache post infusion than previously observed; this delayed adverse event has been observed at about 1% in post-marketing surveillance,[21] and it is unclear if the higher prevalence (>10%) observed in our study is related to the rapid injection.

Hypophosphataemia is increasingly recognised as a complication of intravenous treatment of carbohydrate encapsulated iron moieties, and is mediated by increases in intact FGF23 which acts on the kidney to inhibit phosphate reabsorption and hence urinary phosphate wasting. We observed a profound reduction in serum phosphate levels between baseline and week 2, with some recovery evident by week 4. Whilst 78 patients had biochemical evidence of hypophosphataemia (PO4 <0.8 mmol/L) at 2 weeks (including 32.2% with moderate hypophosphataemia <0.6mmol/L), no patient had severe (<0.3 mmol/L) hypophosphataemia and the lowest observed level was 0.32 mmol/L at 2 weeks, which had risen to 0.37 mmol/L at 4 weeks. We did not record a case of hypophosphataemia causing clinical symptoms. Average phosphate levels increased from two to four weeks, and rose over this period in 73 of the 86 patients in whom both measurements were available. Thirty patients had ongoing biochemical evidence of hypophosphataemia at 4 weeks (PO4 <0.8 mmol/L). The rates of hypophosphataemia reported in our cohort appear similar to previous reports; for example, Franklin Adkinson *et al* recently reported an incidence of hypophosphataemia defined as PO4<0.6 mmmol/L as 38.7% at 2 weeks; using the same definition,[22] we observed hypophosphataemia in 36 of 106 patients (34%). Our post-hoc analyses did not find evidence of an association between phosphate levels at 2 weeks and concurrent experiences of adverse events. Cases of osteomalacia have been reported following recurrent administration of FCM, for example for treatment of recurrent iron deficiency due to chronic bleeding,[23-25] and in such patients clinicians should be mindful of this complication and monitor bone health.

FCM is one of three new generation iron formulations which have entered the market. Ferumoxytol is currently licensed for a 510mg dose over 15 minutes,[26] although safe administration of higher doses in single 30 minute infusions has been reported.[27] Iron isomaltoside is available in Europe and Australia, and permits dosing of up to 1500mg elemental iron in a single infusion. Both of these drugs appear to have a lower risk of biochemical hypophosphataemia than FCM.[22, 28] Based on a collective analysis of all intravenous iron drugs, regulatory guidelines require that intravenous iron only be administered in settings where staff are able to evaluate and manage anaphylactic and anaphylactoid reactions and where resuscitation facilities are available.[29] Our study was not designed to address these concerns, and rapid injections of FCM would still need to occur in the same settings 15 minute infusions are being given.

Our data confirm the rapid efficacy of FCM in replenishing iron stores and increasing haemoglobin. Patients achieved an average haemoglobin increase of almost 20g/L over four weeks, confirming the utility of parenteral iron when subacute correction of anaemia is needed. We observed a homeostatic increase in serum hepcidin in response to iron repletion. Hepcidin concentrations at two and four weeks post infusion were well above thresholds associated with iron repletion,[30] indicating that following a course of parenteral iron, oral iron supplementation is unlikely to be efficiently absorbed[31] and thus likely to be futile and potentially risk gastrointestinal upset.

A key limitation of our study is the absence of a control arm. The study was designed to be able to establish whether rapid injection of FCM would cause SAEs, and with 120 completed patients, we are able to conclude that there were no adverse events meeting the pre-defined

criteria for a Grade 4 or 5 SAEs (i.e. one of death, subject at risk of or required treatment to prevent death, requirement for inpatient hospitalisation, persistent or significant disability or incapacity) with an upper confidence interval band of about 2.5%.[32] Our study therefore provides evidence to enable further exploration of the use of rapid injections of iron in comparative trials.

Figure 1: Changes in biomarkers over course of study

Figure legend: Haemoglobin, ferritin, serum phosphate and (in a subset) hepcidin, at baseline and 2 and 4 weeks following rapid ferric carboxymaltose injection.

Table 1: Adverse events associated with rapid injection of Ferric Carboxymaltose

Timepoint	Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
<1 Hour	Abdominal Pain	0	1	0	0
	Chills	0	1	0	0
	Flushing	52	3	0	0
	Headache	3	0	0	0
	Limb pain	3	0	0	0
	Non Cardiac chest pain	0	0	1	0
	Rash	2	1	1	0
	ECG Changes	2	0	0	0
	Total	**62**	**6**	**2**	**0**
1-24 hours	Abdominal Pain	3	0	0	0
	dizziness	2	0	0	0
	Fatigue	1	1	0	0
	Headache	14	0	0	0
	Fever	4	1	0	0
	Myalgia	3	0	0	0
	Nausea	3	0	0	0
	Rash	0	1	0	0
	Total	**30**	**3**	**0**	**0**
24 hours-2 weeks	Abdominal pain	2	0	0	0
	Angioedema	1	0	0	0
	Back pain	1	0	0	0
	Constipation	1	0	0	0
	Diarrhoea	2	0	0	0
	Facial Pain	1	0	0	0
	Fatigue	1	1	0	0
	Fevers	3	0	0	0
	Headache	10	1	0	0
	Limb pain	1	0	0	0
	Liver impairment	1	0	0	0
	Myalgia	5	1	0	0
	Neck Stiffness	1	0	0	0
	Rash	3	0	0	0
	URTI	3	0	0	0
	Vomiting	2	0	0	0
	myalgia	3	0	0	0
	Candidiasis	1	0	0	0
	Dizziness	1	0	0	0
	Nausea	1	0	0	0
	Non cardiac Chest pain	1	0	0	0

	Total	**45**	**3**	**0**	**0**
2-4 weeks	Epistaxis	1	0	0	0
	Fatigue	1	0	0	0
	Gastroenteritis	1	0	0	0
	Headache	1	0	0	0
	Limb pain	1	0	0	0
	myalgia	2	0	0	0
	Nausea	1	0	0	0
	Rash	2	0	0	0
	URTI	3	0	0	0
	Allergy	1	0	0	0
	Total	**14**	**0**	**0**	**0**

Adverse Events graded according to CTCAE[19] (Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2: Moderate; minimal, local or noninvasive intervention indicated. Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated. Grade 4: Life-threatening consequences; urgent intervention indicated. Grade 5: Death related to AE.)

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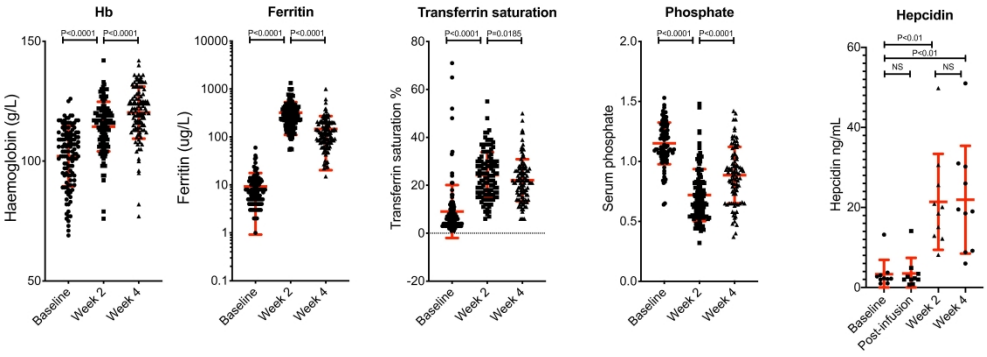

Figure 1

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