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TITLE

Hypophosphataemia after intravenous iron therapy with ferric carboxymaltose – real world experience from a tertiary centre in the UK

Running title

IV iron-induced hypophosphataemia in IDA

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ABSTRACT

Background: Iron deficiency is the most common global cause of anaemia. Intravenous (IV) iron is used to correct iron deficiency anaemia (IDA) where oral iron cannot be used. Despite being effective, certain IV iron formulations cause significant hypophosphataemia. However, current knowledge on the clinical consequences of IV-iron induced hypophosphataemia is broadly anecdotal or limited to isolated case reports.

Aims: To retrospectively examine the incidence and potential clinical consequences of hypophosphataemia post IV ferric carboxymaltose (FCM) in hospitalised patients with IDA (mixed aetiology).

Methods: Data were collected for 162 patients, who received a total of 169 FCM courses during a 2-year audit period. Outcomes included incidence of moderate/severe hypophosphataemia (serum phosphate <0.65 mmol/l) ≤ 90 days post FCM, changes in alkaline phosphatase, need for phosphate replacement, and length of hospital stay.

Results: The incidence of moderate/severe hypophosphataemia post FCM was 33.7%; within this group the rate of severe hypophosphataemia (serum phosphate ≤ 0.32 mmol/l) was 8.8%.

Moderate/severe hypophosphataemia persisted, with 35% of patients having a serum phosphate of <0.65 mmol/L for ≤ 90 days at the last measurement after IV FCM. Intervention with IV phosphate – an average of 4.4 infusions per person – was required in 29.8% of cases with moderate/severe hypophosphataemia. FCM-induced moderate/severe hypophosphataemia was associated with a significantly longer hospital stay ($p < 0.0035$).

Conclusions: Moderate/severe hypophosphataemia is a frequent adverse drug reaction with FCM. In our study, FCM-induced moderate/severe hypophosphataemia was also persistent, often required treatment, and was associated with longer hospital stay.

Key words

Anaemia; ferric carboxymaltose; hypophosphataemia; intravenous; iron; iron deficiency

1 INTRODUCTION

Clinical guidelines recommend the use of intravenous (IV) iron to treat iron deficiency anaemia (IDA) when oral iron formulations cannot be used or when there is a need for rapid delivery of iron.¹⁻⁶ Consequently, IV iron is used across a wide spectrum of clinical scenarios including: 1) chronic disease (e.g., inflammatory bowel disease [IBD], chronic kidney disease [CKD], and chronic heart failure [CHF]); 2) excessive blood loss (e.g., in gastroenterological complications, cancer, surgery, and in the post-partum period); 3) increased demand for iron (e.g., during pregnancy, or in patients receiving erythropoietin stimulating agents [ESAs]).¹⁻⁶

Phosphate is essential for many of the body's vital physiological processes, including the storage and metabolism of energy, muscle contraction, and the maintenance of bone health.^{7,8} Although a mild and transient drop in phosphate concentration is usually not concerning, prolonged and/or severe hypophosphataemia can have important clinical consequences.⁹ If the serum phosphate concentration falls below 0.65 mmol/l – moderate hypophosphataemia – there is a risk of experiencing clinical symptoms including fatigue, proximal muscle weakness, and bone pain.⁹ A serum phosphate concentration of ≤ 0.32 mmol/l indicates severe hypophosphataemia, which can lead to serious complications, such as respiratory failure and cardiovascular problems.¹⁰

Certain IV iron formulations induce hypophosphataemia by stimulating phosphatonin fibroblast growth factor 23 (FGF23) secretion from osteocytes.¹¹⁻¹³ An increased concentration of serum FGF23 inhibits renal phosphate reabsorption (thereby, increasing renal phosphate excretion), and increases the degradation of 1,25-dihydroxyvitamin D, the active form of Vitamin D.¹² A reduced concentration of serum 1,25-dihydroxyvitamin D can lead to hypocalcaemia,^{14,15} which stimulates secondary parathyroid hormone (PTH) excretion in order to maintain serum calcium concentration in the normal range – albeit at the expense of further renal phosphate excretion (triggered by the elevated PTH concentration).^{14,16} Although iron deficiency stimulates FGF23 transcription, this in itself does not usually result in hypophosphataemia because the increased FGF23 production is balanced by increased FGF23 cleavage maintaining a stable concentration of biologically active, intact FGF23.⁹ However, studies have reported that certain IV iron products may inhibit the cleavage of FGF23 within osteocytes, thereby, increasing the concentration of intact FGF23, which promotes hypophosphataemia.^{11,13}

Ferric carboxymaltose (FCM) is a newer generation, high-dose IV iron formulation that is effective and commonly used to treat IDA.¹⁷ A growing body of literature has documented FCM-induced hypophosphataemia in up to 74% of patients.^{11,12,18-22} Hypophosphataemia has also been observed with other IV iron formulations, but the incidence and severity are considerably lower than has been reported with FCM, for reasons that are not entirely clear.^{9,11,19,22,23} For example, two recent randomised controlled trials (RCTs) comparing the incidence of hypophosphataemia between FCM and ferric derisomaltose (FDI) (also known as iron isomaltoside) showed that hypophosphataemia developed in 74.4% of patients treated with FCM, compared with 8.0% of patients treated with FDI.¹²

Consistent with the known effects of hypophosphataemia, clinical consequences of hypophosphataemia following the use of FCM have been described in case reports. Acute symptoms such as severe fatigue, general weakness, respiratory impairment, and gastroenterological side effects have been reported,²⁴⁻²⁶ as well as cases in which IV phosphate supplementation was administered.²⁷ In addition, chronic clinical consequences such as osteomalacia – a softening or weakening of the bone that manifests as bone pain and fractures – have been described in patients receiving large cumulative doses of FCM.²⁸⁻³⁵

The purpose of this study was to assess the incidence of moderate/severe hypophosphataemia and its potential clinical consequences after IV iron therapy with FCM amongst a broad cohort of hospitalised patients at the University College London Hospitals (UCLH) NHS Foundation Trust.

2 METHODS

2.1 Data collection

Two time periods were established to capture potential variations in the clinical practice at UCLH (April 2016–March 2017 and April 2018–December 2018).

The medical notes of 321 in and out patients, who had received at least one course of FCM at UCLH were examined retrospectively. A treatment course consisted of one or two infusions of FCM depending on the estimated iron need. A typical inpatient population comprised patients with multiple comorbidities who were diagnosed with IDA (mixed aetiology) and, subsequently, received IV FCM treatment during their hospitalisation. Outpatients received IV FCM in a daycare setting as part of their treatment for IDA. If the time interval between two FCM infusions was more than 4 weeks, each infusion was analysed as a separate course. Data are presented for FCM treatment courses, unless stated otherwise. All inpatients with ≥ 1 available phosphate measurement post-FCM treatment were included in the analysis. The outpatient cohort was excluded from the analyses as no data relevant to the outcomes of the study existed; data analyses were conducted for inpatients only.

Where available, baseline data for iron administration, demographics, haematinics (haemoglobin [Hb], ferritin, and transferrin saturation [TSAT]), phosphate and related biochemistry (25-hydroxyvitamin D [the storage form of Vitamin D], and alkaline phosphatase [ALP]) were obtained from the patients' medical notes. Phosphate and ALP data were also collected for a period of up to 90 days after the first FCM infusion, and were subsequently analysed at five time points: 0–7 days, 8–14 days, 15–28 days, 29–60 days, and 61–90 days. Data for length of hospital stay after IV FCM treatment were collected for inpatients only, as were the number of hypersensitivity-type adverse drug reactions (ADRs) reported during or immediately after the iron infusion. Where IV phosphate infusions were administered to replenish phosphate levels after FCM treatment, data for the number of infusions were extracted from the medical notes.

2.2 Data analyses

Collected data were separated into two groups depending on the severity of hypophosphataemia at any time following IV FCM treatment: moderate/severe hypophosphataemia (defined as a serum phosphate concentration <0.65 mmol/l) or no/mild hypophosphataemia (defined as a serum

phosphate concentration ≥ 0.65 mmol/l). A serum phosphate concentration of < 0.80 mmol/l is the threshold for mild hypophosphataemia;^{8,9} the threshold of < 0.65 mmol/l for moderate hypophosphataemia in this study aligns with the definition used in previous RCTs;^{11,18} a serum phosphate concentration of ≤ 0.32 mmol/l was the threshold used to define severe hypophosphataemia.

Differences in demographics and baseline clinical characteristics between the two groups were analysed using a two-sided two-sample *t*-test assuming unequal variability. Following FCM treatment, the mean changes from baseline in serum phosphate and ALP were analysed using a two-sided, one-sample *t*-test. In addition, an analysis of covariance (ANCOVA) model including group as a factor and baseline as a covariate was used to analyse: 1) the least squares (LS) mean changes from baseline following FCM treatment, and 2) the difference in the LS mean changes between the group with moderate/severe hypophosphataemia at any time following FCM treatment versus the group with no/mild hypophosphataemia (p-values are two-sided). The length of hospital stay in the two groups was compared using an ANCOVA by ranks with age, weight, and Hb as covariates, and gender, co-morbidities, and group as factors.

2.3 Ethical considerations

This study was approved by the audit department at UCLH. The study adhered to the principles of the Declaration of Helsinki, International Council of Harmonisation, and Good Clinical Practice guidelines.

3 RESULTS

3.1 Patient population

Data flow throughout the study is presented in Figure 1.

Baseline demographics are presented in Table 1. The mean body weight in the group with moderate/severe hypophosphataemia after FCM treatment was significantly lower than in the group with no/mild hypophosphataemia ($p=0.0016$).

Baseline haematinics and biochemical parameters are shown in Table 2. Although the mean baseline serum phosphate concentration for all FCM treatment courses was within the normal range (0.81–1.45 mmol/l), it was significantly lower in the group with moderate/severe hypophosphataemia than in the group with no/mild hypophosphataemia. Similarly, the mean serum baseline ALP concentration was also statistically significantly lower in the group with moderate/severe hypophosphataemia versus the group with no/mild hypophosphataemia (Table 2). There was a trend for lower serum 25-hydroxyvitamin D in the group with moderate/severe hypophosphataemia at baseline, although the difference versus the group with no/mild hypophosphataemia was not clinically significant (Table 2).

3.2 Iron treatment

Across all treatment courses, the mean dose of FCM administered was ~1,000 mg (Table 3). Of the 12/169 (7.1%) treatment courses where ADRs of hypersensitivity occurred during or immediately after the infusion, hydrocortisone treatment was administered in three courses (Table 3).

3.3 Phosphate concentration and the rate of hypophosphataemia

Following treatment with IV FCM, the mean serum phosphate concentration (at any time post-treatment) had significantly decreased compared with the baseline concentration (Table 4). The change from baseline was more substantial in the group with moderate/severe hypophosphataemia (versus the group with no/mild hypophosphataemia), in which the serum phosphate concentration decreased by approximately 50% from baseline following IV FCM treatment (Table 4).

Overall, the rate of moderate/severe hypophosphataemia increased from 3.3% at baseline to 33.7% after treatment with IV FCM (Figure 2a). Among the group with moderate/severe

hypophosphataemia, severe hypophosphataemia was observed after treatment for 8.8% of FCM courses (Figure 2b). Among the group with no/mild hypophosphataemia, mild hypophosphataemia was reported after FCM treatment for 25.0% of courses (Figure 2c).

The presence of moderate/severe hypophosphataemia after FCM treatment was persistent. In the group with moderate/severe hypophosphataemia at any time following FCM, the rate of hypophosphataemia was approximately 70% when evaluated 0–7 days following FCM and approximately 35%, when evaluated at the 61–90 day timepoint (Figure 3).

The use of oral or IV phosphate replacement is illustrated in Table 5. In the group with moderate/severe hypophosphataemia, IV phosphate replacement was required for approximately 30% of FCM courses (with a mean of 4.4 infusions per patient) and oral phosphate was administered for approximately 10% of courses. Phosphate infusions were also administered for 9 FCM treatment courses in the group with no/mild hypophosphataemia (Table 5).

3.4 Phosphate and alkaline phosphatase

In the group with moderate/severe hypophosphataemia, statistically significant decreases from baseline were observed in serum phosphate and increases in ALP following IV FCM treatment (Figure 4). In the group with no or mild hypophosphataemia, statistically significant decreases from baseline were observed for at least one time point in phosphate concentration; there were no significant changes in ALP concentration (data not shown).

3.5 Length of hospital stay

The group with moderate/severe hypophosphataemia had a significantly longer hospital stay than the group with no/mild hypophosphataemia group (Table 6).

4 DISCUSSION

This retrospective study demonstrated a high incidence of moderate/severe hypophosphataemia following IV FCM treatment in a cohort of inpatients requiring IV iron. The data are in accordance with the findings of RCTs and other previous observational studies in patients with IDA of different aetiologies.^{11,12,19,22,23}

Mild, asymptomatic, and transient hypophosphataemia is, generally, not of clinical concern. However, the novel finding from this study is the suggestion that FCM-induced hypophosphataemia can have important clinical consequences. Firstly, the study confirms that hypophosphataemia following FCM administration is often moderate to severe, rather than mild. Secondly, IV phosphate administration was deemed necessary following FCM treatment in a high number of patients with moderate/severe hypophosphataemia, and the number of phosphate infusions given per person was 4.4, on average. Thirdly, FCM-induced hypophosphataemia persisted for a long period of time, and was associated with long-lasting hormonal perturbations and a prolonged hospital stay.

The group with moderate/severe hypophosphataemia showed a significantly lower serum phosphate concentration and body weight at baseline than the group with no/mild hypophosphataemia, suggesting that these two features are risk factors for developing hypophosphataemia (along with FCM treatment). Recommended strategies to avoid FCM-associated morbidity and hospital readmissions include: 1) identifying patients with low phosphate and/or body mass index who are at risk of developing hypophosphataemia after FCM treatment, and 2) reducing the dose of FCM by using a weight-based regimen.³⁶ It has also been suggested that phosphate concentration should be checked before and after FCM administration;²³ this may be particularly important in patients who are likely to require multiple infusions. Indeed, the product label for FCM in the US has been updated to include a requirement to monitor serum phosphate in at-risk patients who require a repeat course of treatment.³⁷

The present study revealed that routine serum phosphate measurement does not take place in a substantial proportion of patients following FCM administration. If serum phosphate is not closely monitored, it is quite possible that other cases of clinically significant hypophosphataemia occurring in clinical practice or in RCTs including FCM have been missed.²³ Consequently, a

change in current clinical practice to include serum phosphate monitoring is necessary to reduce the risk of clinical consequences resulting from FCM-induced hypophosphataemia.

The observed decreases in serum phosphate following FCM treatment are a potential concern for hospitalised patients who are often unwell with multiple co-morbidities, malnourished, and may be exposed to medications known to induce (or exacerbate) hypophosphataemia (such as antacids, diuretics, corticosteroids and antibiotics).³⁸ Consequently, a pre-existing low phosphate concentration is not uncommon in hospitalised populations and, therefore, they may represent a group with higher risk for developing severe hypophosphataemia.⁸ In the present study, IV phosphate was administered in approximately 30% of the FCM courses associated with moderate/severe hypophosphataemia, and some patients with mild hypophosphataemia (phosphate concentration between 0.65–0.79 mmol/l) also received IV phosphate supplementation. This finding indicates that clinicians were concerned about lower serum phosphate levels in such patients. Furthermore, the length of hospital stay was significantly longer (by 1 week) in the group with moderate/severe hypophosphataemia after FCM treatment than in the group with no/mild hypophosphataemia. It is well-documented in the literature that hypophosphataemia can impede recovery in hospitalised patients.^{39,40}

On average, more than four IV phosphate infusions were administered per person in the group with moderate/severe hypophosphataemia, suggesting that this side effect may be resistant to treatment. This observation is in line with the findings of several case reports of FCM-induced hypophosphataemia, where only a transient increase in phosphate concentration occurs in response to phosphate supplementation.^{24,27} Resistance to treatment could possibly be explained by the mechanism of FCM-induced hypophosphataemia – renal phosphate wasting caused by an elevated concentration of FGF23.^{9,11,19,24} Replenishing serum phosphate while the FGF23 remains elevated is unlikely to be effective.

In the present study, moderate/severe hypophosphataemia persisted in approximately 60% of patients with available data up to 60 days, and in approximately 35% of patients with data up to 90 days, after FCM treatment. This further confirms the findings of other studies reporting a high rate of hypophosphataemia up to 40 days after FCM treatment.^{19,22} For example, Detlie et al. found that 13.7% of outpatients with IBD remained hypophosphataemic 6 weeks after FCM treatment,²² while in a study of patients with preserved kidney function and IDA of mixed aetiology by Wolf et

al., the rate of hypophosphataemia was 29% when evaluated 5 weeks after the FCM infusion.¹⁹ Furthermore, in the present study, the ALP concentration was statistically significantly elevated at Days 8–60, indicating that persistent hypophosphataemia following treatment with FCM triggers hormonal perturbations that may have the potential to impact on bone health – an increase in ALP concentration has been observed in patients with osteomalacia.^{41,42} Patient cases developing osteomalacia following prolonged FCM-induced hypophosphataemia have been reported previously.^{28,30,43-45}

This study is limited by its observational and retrospective nature. For example, no data were collected on the type of patient comorbidities or the different IDA aetiologies, which could have contributed to the development of hypophosphataemia. Consequently, it is possible that the observed high rate of hypophosphataemia could have been partly due to other causes; however, previously published studies have reported consistently high rates of hypophosphataemia with FCM.^{11,12,19,22,23} Furthermore, it is not standard practice within the clinical setting to formally measure serum phosphate concentration before FCM treatment and, therefore, it could not be determined if patients were at risk of hypophosphataemia due to a pre-existing low serum phosphate concentration. These limitations highlight the need to identify patients at risk of hypophosphataemia prior to the administration of FCM.

The study could have underestimated the incidence of hypophosphataemia at the follow up points, as no data were available for all patients at each timepoint after FCM treatment – in particular, limited data were available 90 days after FCM treatment. In addition, the study did not implement a standard approach for the treatment of hypophosphataemia, and the impact of potential variances in clinical practice among treating physicians on the results cannot be excluded. Furthermore, the study did not capture FGF23 concentration to confirm the underlying mechanism of hypophosphataemia, nor did it include a control group of patients who did not receive FCM. Although the mechanism of FCM-induced hypophosphataemia has been well described in the literature,^{11,12,19,36} prospective research is required to further explore hypophosphataemia and its clinical consequences in hospitalised patients with multiple comorbidities, as well as in outpatients. Indeed, a prospective controlled trial to confirm these effects is currently in development. Finally, although no data were available on the symptoms that patients experienced, our study does show that FCM-induced hypophosphataemia was of sufficient clinical concern to administer phosphate supplementation in a vulnerable patient population.

In conclusion, this retrospective study confirmed that moderate/severe hypophosphataemia is a side effect of FCM treatment that occurs at a high rate. FCM-induced hypophosphataemia can be persistent, can have serious clinical consequences requiring phosphate supplementation, and may impede the recovery of hospitalised patients.

AUTHORSHIP STATEMENT

Guarantor of the article

Farooq Rahman

Specific author contributions

Konstantinos C. Fragkos, Vinay Sehgal: conception of idea, study design, data collection, analysis, writing of the manuscript. Jennifer Rogers, Sithhipratha Arulrajan, Pranavan Pavanerathan, John Barragry, Gregory M. Sebeos-Rogers: data collection and writing of the manuscript. Shameer J. Mehta, Simona Di Caro, Farooq Rahman: conception of study, supervision of study, study design, writing of manuscript.

All authors approved the final version of this article, including the authorship list.

STATEMENTS OF INTEREST

1. Authors' declaration of personal interests:

Konstantinos C. Fragkos, Shameer J. Mehta, and Farooq Rahman have served as a speaker, a consultant, or an advisory board member for Pharmacosmos UK Ltd. Konstantinos C Fragkos has received research funding from Pharmacosmos UK Ltd. Vinay Sehgal, Jennifer Rogers, Sithhipratha Arulrajan, Pranavan Pavanerathan, John Barragry, Gregory M. Sebeos-Rogers, and Simona Di Caro have no conflicts of interest.

2. Declaration of funding interests:

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ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received. The study conformed to the US Federal Policy for the Protection of Human Subjects.

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TABLES

Table 1: Baseline demographics

	All patients (N=162)	Patients with moderate/severe hypophosphataemia (N=54)	Patients with no/mild hypophosphataemia (N=108)	p-value
Age, years, mean (SD)	57.1 (23.6)	58.4 (23.7)	56.4 (23.7)	NS
Gender, n (%)				
Female	100 (61.7)	33 (61.1)	67 (62.0)	–
Male	62 (38.3)	21 (38.9)	41 (38.0)	–
Weight, kg (n=90)		(n=36)	(n=54)	
Mean (SD)	66.8 (21.6)	58.9 (14.3)	72.0 (24.0)	0.0016

Baseline data were separated into two groups depending on whether moderate/severe hypophosphataemia (defined as a serum phosphate concentration <0.65 mmol/l) or no/mild hypophosphataemia (defined as a serum phosphate concentration ≥ 0.65 mmol/l) – was present at any time following FCM treatment.

P-values for the group with moderate/severe hypophosphataemia versus the group with no/mild hypophosphataemia were calculated using a two-sided two-sample *t*-test assuming unequal variability.

NS, not significant; SD, standard deviation.

Table 2: Baseline clinical characteristics

	All FCM treatment courses (N=169)	Courses reporting moderate/severe hypophosphataemia (N=57)	Courses reporting no/mild hypophosphataemia (N=112)	p-value
Hb, g/l	(n=166)	(n=56)	(n=110)	
Mean (SD)	90.7 (18.1)	92.0 (17.8)	90.1 (18.4)	NS
Ferritin, µg/l	(n=133)	(n=45)	(n=88)	
Mean (SD)	215.3 (345.5)	259.4 (372.4)	192.7 (330.8)	NS
TSAT, %	(n=151)	(n=51)	(n=100)	
Mean (SD)	11.3 (7.7)	11.6 (8.0)	11.2 (7.6)	NS
Phosphate, mmol/l	(n=152)	(n=52)	(n=100)	
Mean (SD)	1.1 (0.3)	1.0 (0.3)	1.1 (0.3)	0.0103
Time from baseline phosphate to FCM treatment, days	(n=71)	(n=21)	(n=50)	
Mean (SD)	28.4 (81.2)	19.5 (44.3)	33 (94.8)	–
25-hydroxyvitamin D, nmol/l	(n=71)	(n=21)	(n=50)	
Mean (SD)	45.4 (30.9)	41.1 (21.9)	47.3 (34.0)	NS
ALP, IU/l	(n=151)	(n=49)	(n=102)	
Mean (SD)	114.9 (105.0)	90.8 (40.4)	126.5 (123.2)	0.0090

Baseline data were separated into two groups depending on whether moderate/severe hypophosphataemia (defined as a serum phosphate concentration <0.65 mmol/l) or no/mild hypophosphataemia (defined as a serum phosphate concentration ≥0.65 mmol/l) – was present at any time following FCM treatment.

P-values for the group with moderate/severe hypophosphataemia versus the group with no/mild hypophosphataemia were calculated using a two-sided two-sample *t*-test assuming unequal variability.

ALP, alkaline phosphatase; FCM, ferric carboxymaltose; Hb, haemoglobin; IU, international units; NS, not significant; SD, standard deviation; TSAT, transferrin saturation.

Table 3: Iron treatment

	All FCM treatment courses (N=169)	Courses reporting moderate/severe hypophosphataemia (N=57)	Courses reporting no/mild hypophosphataemia (N=112)
Iron dose, mg	(n=133) [†]	(n=47)	(n=86)
Mean (SD)	1,041.5 (330.0)	1,010.6 (303.8)	1,058.4 (344.0)
Hypersensitivity ADRs reported, n (%)	12 (7.1)	4 (7.0)	8 (7.1)
Courses requiring hydrocortisone intervention, n (%)	3 (1.8)	1 (1.8)	2 (1.8)

Moderate/severe hypophosphataemia was defined as a serum phosphate concentration <0.65 mmol/l; no/mild hypophosphataemia was defined as a serum phosphate concentration ≥0.65 mmol/l.

[†]A total of 169 courses of FCM were administered, but the mean iron dose was not recorded for 36 courses.

ADR, adverse drug reaction; FCM, ferric carboxymaltose; SD, standard deviation.

Table 4: Phosphate concentration following treatment with FCM

	All FCM treatment courses (N=169)	Courses reporting moderate/severe hypophosphataemia (N=57)	Courses reporting no/mild hypophosphataemia (N=112)
Phosphate, mmol/l			
Mean (SD)	0.8 (0.3)	0.5 (0.1)	1.0 (0.3)
Change from baseline in phosphate, mmol/l, mean (SD) [†]	-0.275 (0.353) (p<0.001)	-0.521 (0.262) (p<0.001)	-0.148 (0.326) (p<0.001)
LS mean change from baseline [‡]		-0.5782	-0.1178
LS mean difference between groups [‡]		-0.4604 (95% CI: -0.5407, -0.3801; p<0.001)	

Moderate/severe hypophosphataemia was defined as a serum phosphate concentration <0.65 mmol/l; no/mild hypophosphataemia was defined as a serum phosphate concentration ≥0.65 mmol/l.

[†]P-values versus baseline were calculated using a two-sided, one-sample *t*-test.

[‡]Calculated from ANCOVA model including a factor for group, with baseline included as a covariate; the p-value is two-sided.

ANCOVA, analysis of covariance; CI, confidence interval; FCM, ferric carboxymaltose; LS, least squares; SD, standard deviation.

Table 5: Phosphate supplementation following treatment with FCM

	All FCM treatment courses (N=169)	Courses reporting moderate/severe hypophosphataemia (N=57)	Courses reporting no/mild hypophosphataemia (N=112)
Treated with phosphate, n (%)	(n=33)	(n=21)	(n=12)
IV phosphate	26 (15.4)	17 (29.8)	9 (8.0)
Oral phosphate	9 (5.3)	6 (10.5)	3 (2.7)
Number of phosphate infusions/person, mean (SD)	(n=25) 3.4 (3.1)	(n=16) 4.4 (3.5)	(n=9) 1.6 (1.0)

Moderate/severe hypophosphataemia was defined as a serum phosphate concentration <0.65 mmol/l; no/mild hypophosphataemia was defined as a serum phosphate concentration ≥ 0.65 mmol/l.

FCM, ferric carboxymaltose; IV, intravenous; SD, standard deviation.

Table 6: Length of hospital stay following treatment with FCM

	Courses reporting moderate/severe hypophosphataemia (N=57)	Courses reporting no/mild hypophosphataemia (N=112)	p-value
Length of hospital stay, days, mean (SD)	18 (19.8)	10.9 (13.4)	0.0035 [†]

Moderate/severe hypophosphataemia was defined as a serum phosphate concentration <0.65 mmol/l; no/mild hypophosphataemia was defined as a serum phosphate concentration ≥0.65 mmol/l.

[†]P-values were calculated using an ANCOVA by ranks with age, weight, and Hb as covariates, and gender, co-morbidities, and group as factors.

ANCOVA, analysis of covariance; CI, confidence interval; Hb=haemoglobin; NS, not significant; SD, standard deviation.

FIGURE LEGENDS

Figure 1: Data flow throughout the study

Data were separated into two groups depending on whether moderate/severe hypophosphataemia (defined as a serum phosphate concentration <0.65 mmol/l) or no/mild hypophosphataemia (defined as a serum phosphate concentration ≥ 0.65 mmol/l) – was present at any time following FCM treatment.

FCM, ferric carboxymaltose; UCLH, University College London Hospitals.

Figure 2: Rate of hypophosphataemia before and after treatment with FCM

Moderate/severe hypophosphataemia was defined as a serum phosphate concentration <0.65 mmol/l; no/mild hypophosphataemia was defined as a serum phosphate concentration ≥ 0.65 mmol/l.

FCM, ferric carboxymaltose.

Figure 3: Rate of hypophosphataemia over time in the group with moderate/severe hypophosphataemia at any time following treatment with FCM

FCM, ferric carboxymaltose.

Figure 4: Phosphate and ALP following treatment with FCM in the group with moderate/severe hypophosphataemia

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus baseline.

[†]Baseline values are mean (SD).

Moderate/severe hypophosphataemia was defined as a serum phosphate concentration < 0.65 mmol/l; no/mild hypophosphataemia was defined as a serum phosphate concentration ≥ 0.65 mmol/l.

P-values versus baseline were calculated using a two-sided, one-sample *t*-test.

ALP, alkaline phosphatase; CI, confidence interval; FCM, ferric carboxymaltose; IU, international unit; LS, least squares; SD, standard deviation.







