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Acute and sub-acute effect of ferric carboxymaltose on inflammation and adhesion molecules in patients with predialysis chronic renal failure

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ABSTRACT

Background: Treatment with parenteral iron causes oxidative stress, inflammation and endothelial dysfunction. Ferric carboxymaltose (FCM) is a new preparation of non-dextran iron which, due to its pharmacokinetics and stability, may induce less toxicity than other iron molecules. The aim of this study was to analyse the effect of FCM on inflammation and adhesion molecules in chronic kidney disease (CKD). **Methods:** Forty-seven patients with predialysis CKD and iron-deficiency anaemia received a single dose of FCM (15mg/kg, maximum dose 1 gram). At baseline and after 60 minutes (acute effect) and after 3 weeks and 3 months (sub-acute effect), we determined inflammatory markers: C-reactive protein (CRP), interleukin-6 (IL-6) and endothelial dysfunction: intercellular adhesion molecule (ICAM) and vascular adhesion molecule (VCAM). **Results:** Treatment with FCM was associated with a significant increase in haemoglobin levels: 10 (0.7) vs. 11.4 (1.3)g/dl, $P<.0001$. CRP, IL-6, ICAM and VCAM levels did not correlate with baseline haemoglobin or ferritin levels and there was no relationship between changes in these markers and those of haemoglobin after administration of FCM. No significant, acute or sub-acute changes occurred in any of the inflammatory or endothelial markers studied. Statin therapy was associated with lower VCAM concentrations. **Conclusions:** Treatment with high doses of FCM in patients with predialysis CKD has no proinflammatory effect and does not alter levels of adhesion molecules ICAM and VCAM in this population.

Keywords: Ferric carboxymaltose. Chronic kidney disease. Inflammation. Adhesion molecules.

Efecto agudo y subagudo de la carboximaltosa férrica sobre la inflamación y moléculas de adhesión en pacientes con insuficiencia renal crónica prediálisis

RESUMEN

Antecedentes: El tratamiento con hierro parenteral provoca estrés oxidativo, inflamación y disfunción endotelial. La carboximaltosa férrica (CMF) es un nuevo preparado de hierro no dextrano que, por sus características farmacocinéticas y estabilidad, podría inducir menor toxicidad que otras moléculas de hierro. El objetivo de este estudio fue analizar el efecto de la CMF sobre la inflamación y moléculas de adhesión en la enfermedad renal crónica (ERC). **Métodos:** Cuarenta y siete pacientes con ERC prediálisis y anemia ferropénica recibieron una dosis única de CMF (15 mg/kg, dosis máxima 1 gramo). De forma basal, a los 60 minutos (efecto agudo), y a las 3 semanas y 3 meses (efecto subagudo), se determinaron marcadores de inflamación: proteína C reactiva (PCR) e interleucina 6 (IL-6), y de disfunción endotelial: moléculas de adhesión intercelular (ICAM) y vascular (VCAM). **Resultados:** El tratamiento con CMF se asoció a un incremento significativo de los niveles de hemoglobina: 10 (0,7) vs. 11,4 (1,3) g/dl, p < 0,0001. Los niveles de PCR, IL-6, ICAM y VCAM no se correlacionaron con los niveles basales de hemoglobina ni ferritina, y no se observó ninguna relación entre los cambios en estos marcadores y los de hemoglobina después de la administración de CMF. No se observaron cambios significativos ni de forma aguda o subaguda en ninguno de los marcadores inflamatorios o endoteliales estudiados. El tratamiento con estatinas se asoció a menores concentraciones de VCAM. **Conclusiones:** El tratamiento con dosis elevadas de CMF en pacientes con ERC prediálisis no tiene efecto proinflamatorio ni modifica los niveles de moléculas de adhesión ICAM y VCAM en esta población.

Palabras clave: Carboximaltosa férrica. Insuficiencia renal crónica. Inflamación. Moléculas de adhesión.

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INTRODUCTION

Anaemia in chronic kidney disease (CKD) has a multifactorial origin with iron deficiency being one of the main mechanisms,

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and a prevalence of about 50% according to studies.[1] This deficiency also implies a risk of arteriosclerosis,[2,3] since there is a defect in iron-containing protein production with antioxidant capacity.

It has been observed how iron-deficient patients have a higher level of adhesion molecules, which are *per se* a risk factor for developing arteriosclerosis[4] and are independent factors of cardiovascular death.[5] In CKD, inflammatory markers and adhesion molecules expression are increased and there is an inverse relationship with renal function: the lower the glomerular filtration (GF), the higher its expression.[6] This relationship is maintained in haemodialysis.[7] In the population with normal renal function, the correction of iron deficiency decreases the expression of these molecules,[8] although there are no studies in predialysis CKD patients.

Treatment with intravenous iron is safe and effective in correcting anaemia in patients with CKD in which iron requirements are increased. However, there are some studies, especially on dialysis, that demonstrate that the aforementioned treatment increases the inflammatory state;[9-11] however, in other studies that use different preparations at different doses and frequencies of administration, the aforementioned increase is not observed.[12-16] There is little evidence of the action of iron on the expression of adhesion molecules. Experimental studies examining the effect of different iron molecules on mononuclear cells of patients on haemodialysis demonstrate there is a lesion and an activation of these cells.[17,18]

It has been suggested that differences in the pharmacological characteristics of iron preparations and administration dosage (dose and administration intervals) of the iron administered may involve variations in the inflammatory effect[19-22] and on adhesion molecules.

Ferric carboxymaltose (FCM) is a new generation of non-dextran iron, which may be administered quickly and at high doses; it involves a controlled release of iron to the tissues and has minimal side effects.[23-25] Due to these characteristics, it has been suggested that this iron molecule would have less effect on inflammation and adhesion molecules. In fact, in experiments, it has been shown that FCM, compared with other iron preparations with lower molecular weight, does not induce oxidative stress or increase inflammation.[22]

The aim of our study was to analyse the effect of FCM administration in predialysis CKD patients with iron deficiency on adhesion molecules and inflammation.

METHODS

Study population

50 patients were recruited from the Nephrology department's outpatient service of the Hospital Universitari Joan XXIII in Tarragona. They were above 18 years of age, had predialysis CKD and presented the following inclusion criteria: serum haemoglobin <11g/dl, serum ferritin <100ng/ml and/or transferrin saturation index <20%. Patients excluded were those who in the previous three months had received oral iron or blood transfusion or who had bleeding, infection or active acute inflammatory process and a history of hypersensitivity to treatment with intravenous iron.

Of the initial 50 patients, 3 were excluded (2 due to gastrointestinal bleeding and 1 due to active infection during follow-up), and therefore, the final study population consisted of 47 patients.

This study was approved by the hospital ethics committee and all patients signed the informed consent.

Study design

This was a prospective study that lasted for 18 months (beginning in April 2010 and ending in October 2011). Patients received a single dose of FCM (Ferinject®) at 15mg/kg (maximum 1g) diluted in 250cc of saline solution with an infusion time of 30 minutes.

Determination of clinical variables

Some cardiovascular risk factors such as hypertension, dyslipidaemia and obesity were determined.

Arterial hypertension (HTN): blood pressure was determined on three occasions during the procedure (with three measurements in each of them) for assessment of haemodynamic tolerance during the process. We used a validated automatic device (Omron 705CP, Healthcare GmbH, Hamburg, Germany). HTN was defined as systolic blood pressure of 140 mmHg or higher, diastolic blood pressure of 90mmHg or higher, or treatment with antihypertensive drugs.

Obesity: body mass index (BMI) expressed as weight (kg)/height (square metre) was calculated. Obesity was defined as BMI>30kg/m².

Dyslipidaemia: was defined as total cholesterol greater than 240mg/dl or being on statin therapy.

Diabetes mellitus: was defined as fasting plasma glucose above 126mg/dl or patients treated with oral anti-diabetic drugs and/or insulin.

Biochemical determinations

At baseline, 60 minutes after administration of FCM (acute effect), and after 3 weeks and 3 months of treatment (sub-

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acute effect), the determination of haemoglobin (Hb) and ferrokinetic parameters (ferritin, transferrin saturation index [TSI] was carried out by conventional methods and inflammatory markers: ultrasensitive C-reactive protein (CRP), interleukin 6 (IL-6) and adhesion molecules: soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cellular adhesion molecule-1 (sVCAM-1). Levels of IL-6 were determined using the commercial kit Human IL-6 Quantikine HS High Sensitivity (R&D Systems, Lille, France). The N High Sensitivity CRP kit was used to determine CRP (Dade Bering, Newark, USA). Levels of ICAM and VCAM were determined by the Quantikine® ELISA kit (R&D Systems, Minneapolis, USA).

In all patients, routine methods were used to determine levels of creatinine and GF through the formula MDRD-4.

STATISTICAL ANALYSIS

Statistical analysis was performed using the SPSS v. 15 software. Ultrasensitive CRP values were not distributed normally and were therefore transformed logarithmically. The verification or rejection of the hypothesis of normality of continuous variables was performed with the Shapiro-Wilk test. The association between nominal variables was studied by contingency tables and Fisher's exact probability test. To analyse the association between a continuous variable and a nominal variable, the Mann-Whitney "U" test or the Kruskal-Wallis test were used in accordance with whether or not it was dichotomous. We used Spearman's correlation coefficient to measure the linear association between two continuous variables. For analysis involving repeated measurements of continuous variables, we used analysis of the variance for repeated measurements with the criterion of Wilks' lambda. The level of statistical significance was set at $P<.05$ in a two-tailed test.

RESULTS

Population characteristics

This is an older population (mean age 72 years) with CKD: 13 patients in stage 3; 27 in stage 4 (57.4%) and 7 non-dialysis patients in stage 5 CKD. The aetiology of the CKD was of vascular origin (48.9%), followed by diabetic nephropathy (25.5%); other causes included: interstitial/polycystic kidney disease (6.4%), glomerular (4.3%) and unknown origin (14.9%).

All patients were hypertensive, overweight (mean BMI of 29kg/m²), 75% were dyslipidaemic and 40% had diabetes.

The characteristics of the population are summarised in Table 1.

Effect of ferric carboxymaltose on anaemia

After treatment with FCM, we observed a significant increase in levels of Hb, ferritin and TSI (Table 2).

Acute effect of ferric carboxymaltose on adhesion molecules and inflammation

No significant differences were observed between the baseline levels and levels after 60 minutes of VCAM and ICAM treatment, and no significant differences were observed in inflammatory markers (Table 3).

Sub-acute effect of ferric carboxymaltose on adhesion molecules and inflammation

We did not observe any significant changes in adhesion molecules or inflammatory markers after 3 weeks or 3 months of treatment with FCM. In an analysis differentiated in accordance with the CKD stage: stage 3 vs. stage 4 + 5, no significant changes were observed in any of the markers analysed. Albumin levels remained unchanged throughout the study.

Table 1. Clinical variables of the population.

Age (years)	72 (11.6)
Sex (M/F)	23/24
BMI (kg/m²)	29.3 (4.5)
HTN	47 (100%)
SBP (mmHg)	150.5 (31.6)
DBP (mmHg)	71.3 (14.6)
Use of ACE inhibitor/ARBs	28 (59.6%)
DM	19 (40.4%)
Dyslipidaemia	35 (74.5%)
Use of statins	26 (53.3%)
Use of ESA	23 (48.9%)
Creatinine (mg/dl)	2.56 (0.95)
GF (ml/min/1.73m²)	26.1 (10.4)

ESA: erythropoiesis-stimulating agents; ARBs: angiotensin II receptor antagonists; DM: diabetes mellitus; GF: glomerular filtration rate; M: male; AHT: arterial hypertension; ACE inhibitors: angiotensin converting enzyme inhibitors; BMI: body mass index; F: female; DBP: diastolic blood pressure; SBP: systolic blood pressure.

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Table 2. Effect of ferric carboxymaltose on anaemia.

	Baseline	3 weeks	3 months	*P*
Haemoglobin (g/dl)	10.0 (0.71)	10.8 (0.87)	11.4 (1.3)	<0.0001
Ferritin (ng/ml)	67.8 (61.7)	502.5 (263.3)	230 (144.6)	<0.0001
TSI (%)	14.6 (6.4)	28.9 (10.0)	25.6 (12.7)	<0.0001

TSI: transferrin saturation index.

After adjusting the effect of treatment with FCM and various parameters such as the presence of diabetes mellitus, dyslipidaemia, the use of erythropoiesis stimulating agents, the use of angiotensin converting enzyme inhibitors and/or angiotensin II receptor antagonists and statins, we only observed that statin use changed the response of the adhesion molecules on treatment with FCM. VCAM levels were lower in patients treated with statins than in untreated patients (*P*=.02). In addition, they significantly increased in untreated patients, while they remained unchanged in treated patients (*P*=.02) (Table 4). No significant differences were perceived in ICAM levels.

Lastly, we examined the influence of treatment with paricalcitol on the effect of FCM on inflammatory markers and endothelial cells, without perceiving significant differences between treated and untreated patients.

The effect of FCM on adhesion molecules and inflammation is summarised in Table 3.

The relationship between anaemia, inflammatory markers and adhesion molecules

No correlation was observed between baseline levels of Hb, ferritin, CRP, IL-6, VCAM or ICAM, or between the percentage of change in levels of Hb, CRP, IL-6, VCAM and ICAM after 3 weeks and 3 months.

DISCUSSION

The result of our study shows that in patients with predialysis CKD and iron deficiency anaemia, treatment with FCM does not induce inflammation or cause an increase in adhesion molecules.

Iron deficiency anaemia in CKD patients is a major problem because of its high prevalence and its contribution to the morbidity and mortality associated with CKD.[5] It is considered one of the non-traditional cardiovascular risk factors[24] and, although less well-known, it is also considered an independent risk factor in the development of arteriosclerosis, probably due to a defect in the production of other Fe^{2+}-containing proteins such as peroxidases, catalases involved in preventing the latter.[25]

Patients with iron deficiency anaemia have higher levels of adhesion molecules.[8] These molecules are directly involved in the initiation and aggravation of arteriosclerotic lesions.[26] In CKD, there is an overexpression of these molecules, which are higher the lower the GF, and they remain high in the population on renal replacement therapy. High levels of these molecules are associated with malnutrition, inflammation and cardiovascular disease; this suggests that there is a relationship between vascular activation, systemic inflammation and uraemic toxicity. Lastly, CKD is considered to be an inflammatory state involved in different complications of CKD, such as malnutrition and accelerated atherosclerosis.[27-29]

Table 3. Acute and sub-acute effect of ferric carboxymaltose on inflammatory markers and adhesion molecules.

	Baseline	1 hour	3 weeks	3 months	*P*
VCAM(ng/ml)	1281.5 (695.1)	1325.2 (684.4)	1281.6 (698)	1262.4 (713.9)	ns
ICAM (ng/ml)	340.7 (112.0)	343.6 (123.5)	336.8 (117.8)	348.3 (104.2)	ns
Log CRP	0.60 (0.55)	0.48 (0.54)	0.59 (0.54)	0.57 (0.59)	ns
IL-6 (pg/ml)	4.74 (4.76)	4.57 (7.06)	4.49 (4.5)	4.0 (3.27)	ns

ICAM: intercellular adhesion molecules; IL-6: interleukin 6; ns: not significant; CRP: C-reactive protein; VCAM: vascular cell adhesion molecules.

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Table 4. Influence of treatment with statins in the response of adhesion molecules to ferric carboxymaltose.

	Baseline	3 weeks	3 months
VCAM (ng/ml)			
no statins	1479.9 (883.7)	1481.5 (913.6)	1565.8 (984.5)
statins	1151.4 (482.3)	1150.6 (444.9)	1039.6 (222.6)
ICAM (ng/ml)			
no statins	344.5 (94.8)	351.1 (105.3)	366.8 (132.7)
statins	339.6 (127.2)	325.5 (129.6)	333.5 (76.8)

ICAM: intercellular adhesion molecules; VCAM: vascular cell adhesion molecules.

Ferric carboxymaltose and inflammation

It has been suggested that treatment with parenteral iron could contribute to morbidity and mortality in patients with CKD due to increased oxidative stress and inflammation. In our study, treatment with FCM did not have an acute or a short-term proinflammatory effect.

One of the possible mechanisms responsible for the neutral effect of FCM on inflammation could be that correcting anaemia would improve or rather counteract the inflammatory stimulus of FCM. In fact, there are studies in patients with anaemia treated with erythropoiesis-stimulating agents in which, after an improvement in Hb figures, there is a decrease of inflammatory parameters,[30] even if taking iron.[31] By contrast, in our study, we did not find a correlation between changes in Hb levels and inflammatory parameters, which suggests that the neutral effect of treatment with FCM on inflammation would not be mediated by the improvement of anaemia.

Another possible explanation could be the characteristics of the FCM molecule. Iron preparations of low molecular weight and low thermokinetic stability (iron gluconate, iron sucrose) cause an abrupt rise in serum iron, with transferrin oversaturation and more free iron, which determines an increase in inflammatory molecules. By contrast, ferric carboxymaltose is a macromolecular carbohydrate-iron hydroxide complex, designed to allow a controlled release of iron in the cells of the reticuloendothelial system, minimising the risk of releasing large amounts of ionic iron in serum. In a study conducted in rats,[22] we compared the effect of different iron preparations, including carboxymaltose, on inflammation and oxidative stress, concluding that the aforementioned molecule would induce less inflammation than other preparations.

Lastly, we must mention the lack of a proinflammatory effect of FCM with high doses of this molecule used in this study. In most publications, intravenous iron doses are low compared to those of our study, and some also advocate the slow administration of the product in order to minimise the aforementioned proinflammatory effect. We have not observed this effect despite using large doses (about 1 gram on average) in a short interval of time (maximum 30 minutes). However, given that there are no studies with a follow-up time longer than three months, the implications of long-term use of FCM on inflammatory status is unknown.

Ferric carboxymaltose and adhesion molecules

There are few studies that analyse the effect of parenteral iron administration on adhesion molecules in patients with CKD and iron deficiency anaemia.

In the population with normal renal function, it has been observed that administration of oral iron causes a decrease in VCAM, but not ICAM.[8]

Treatment with four intravenous iron preparations (ferric gluconate, iron sucrose, iron dextran and FCM) causes an increase in the expression of ICAM-1, reactive oxygen species and apoptosis in the mononuclear cells of patients with stage 5 CKD and in haemodialysis patients, regardless of the iron used. By contrast, in our study, treatment with FCM had no effect on the levels of adhesion molecules, as has been described with iron sucrose on endothelial function in patients on haemodialysis[16] or peritoneal dialysis.[15]

The mechanism by which FCM would not produce endothelial lesion could also be related to the characteristics of the molecule itself, with a lower release of ionic iron in serum and lower endothelial lesion.

Lastly, we must note the effect of statins on adhesion molecules. The relationship between arteriosclerosis and inflammation is known,[32] as well as that statins reduce systemic inflammation and improve endothelial function.[33,34] In our study, we observed lower levels of VCAM in patients

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who were on lipid-lowering treatment, which suggests that statins may counteract the stimulation of treatment with FCM on the aforementioned adhesion molecule.

Limitations of the study

The number of patients included in the study was small and the follow-up time was short. Studies with larger numbers of patients and longer follow-up periods are necessary to confirm the lack of effect of FCM on inflammation and adhesion molecules in this population.

Our study did not evaluate endothelial function. However, plasma concentrations of adhesion molecules analysed correlate with the expression of these molecules in the surface of the endothelial cells,[35] they reflect endothelial activation and vascular inflammation[36] and are considered to be markers of endothelial dysfunction.

In conclusion, treatment with high doses of FCM in patients with predialysis CKD has no proinflammatory effect and does not change the levels of adhesion molecules in these patients. Concomitant treatment with statins is associated with a lower concentration of these molecules.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

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