

The pharmacology and safety profile of ferric carboxymaltose (Ferinject®): structure/reactivity relationships of iron preparations

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■ ABSTRACT

Ferric carboxymaltose (FCM, marketed as Ferinject®) is a new intravenous iron preparation. It combines the positive characteristics of iron dextran and iron sucrose but is not associated with dextran-induced hypersensitivity reactions and can be given in much higher doses than iron sucrose or iron gluconate. The chemical characteristic of the iron-carbohydrate complex means that iron is released slowly, avoiding toxicity and oxidative stress. Up to 1000 mg iron can be given in a single administration of FCM, and this can be given by rapid infusion over 15 minutes. The reduced administration time, coupled with the fact that a test dose is not required (in contrast to iron dextran and iron sucrose) and the fact that a large amount of iron can be given in one dosage, offer convenience for patients and potential cost savings for healthcare providers.

Key-Words:

Antianaemic drug; iron carboxymaltose; metabolism; pharmacokinetics; reactivity.

■ INTRODUCTION

A new form of intravenous iron, ferric carboxymaltose (FCM, marketed as Ferinject®) has been developed to combine the positive characteristics of iron dextran and iron sucrose. There was a need for

such an iron preparation because of the problems and limitations associated with iron dextran and iron sucrose. FCM was therefore developed to have a better safety and tolerability profile than existing products. Specifically, it avoids dextran-induced hypersensitivity reactions (DIAR) and overcomes the low-dosage limitations of iron sucrose and iron gluconate. It has a neutral pH and a physiological osmolality and can be given by rapid infusion. FCM exhibits low reactivity with molecules in blood and living cells and therefore causes little toxicity. It has a structure similar to ferritin and causes iron to be deposited in the reticuloendothelial system (RES) of the liver. It can therefore provide iron without inducing oxidative stress.

■ CHEMICAL CHARACTERISTICS AND METABOLISM OF FCM

The active pharmaceutical ingredient (API) of FCM is water soluble and the final product (FP) Ferinject® is a colloidal solution. FCM comprises a macromolecular iron-hydroxide complex of polynuclear iron (III) hydroxide in a carbohydrate shell. The complex has a molecular weight of around 150,000 Daltons. This means that little of the product is lost through renal elimination, unlike other smaller iron complexes.

Once in the body, iron is released gradually, avoiding the acute toxicity of many other iron compounds

but allowing large amounts of iron to be delivered. This results in a much wider therapeutic window. For example, the LD₅₀ (i.e. the dose that kills 50% of experimental mice) is just 11 mg Fe/kg for intravenous administration of the common salt, iron sulphate (FeSO₄), around 50 for oligonuclear complexes such as Fe(II)EDTA and Fe(III) gluconate, >200 for iron sucrose, >2500 for iron dextran and iron dextran¹. For FCM the LD₅₀ is >1000 mg Fe/kg body weight.

Due to the stability of the complex, FCM does not release ionic iron under physiological conditions. The iron hydroxide is tightly bound within a carbohydrate cage (Fig. 1).



Figure 1

Iron carboxymaltose (FCM) showing the iron oxyhydroxide core contained in the carbohydrate shell.

Therefore the iron hydroxide core, with its carbohydrate shell, is taken up by macrophages and enters the lysosomes where Fe³⁺ can be converted into Fe²⁺ as required. The Fe²⁺ is released by a divalent metal transporter (DMT1) then by ferroportin and taken up by transferrin after oxidation by ceruloplasmin (Fig. 2).

In less stable complexes, iron is released rapidly from the complex causing high levels of transferrin saturation (60-100%) and therefore non-transferrin-bound iron (NTBI). This NTBI, outside the macrophage, is highly toxic. Small amounts of iron in the serum (about 3 mg/l) can result in almost complete transferrin saturation.

Following a 100mg iron dose from FCM (Ferinject®), iron sucrose (Venofer®) or iron gluconate

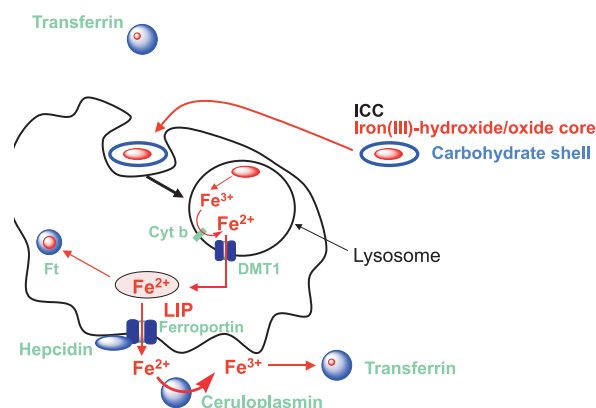


Figure 2

Metabolism and toxicity of iron-hydroxide carbohydrate complexes (ICC).

(Ferrerle®) different patterns of transferrin saturation are observed. With FCM, unbound apo-transferrin predominates, with iron sucrose, more monoferric transferrin (Fe-Tf) is observed, whereas with iron gluconate, both Fe-Tf and diferric transferrin (Fe₂-Tf) is observed after 4 hours incubation (Fig. 3).

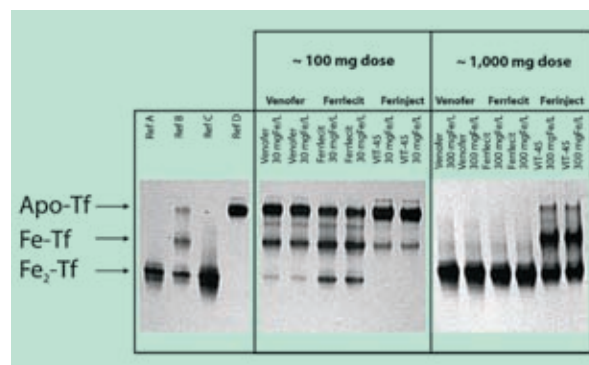


Figure 3

Reactivity of iron carboxymaltose (FCM, Ferinject®), iron sucrose (Venofer®) and iron gluconate (Ferrerle®) with transferrin (incubation time 4 hours).

Following a 1000mg iron dose, iron sucrose and gluconate cause oversaturation of transferrin, while with FCM a balance of apo-transferrin, Fe-Tf and Fe₂-Tf is observed. This higher reactivity of iron sucrose and gluconate is reflected in the clinical characteristics and recommended doses, since the maximum single dose for iron gluconate is 62.5-125mg iron, that for iron sucrose is 200-500mg iron, while for FCM up to 1000 mg iron can be given in a single dose.

SAFETY AND TOLERABILITY OF IRON PREPARATIONS

Oversaturation of transferrin following rapid administration of iron sucrose (faster than the recommended rate) leads to transient adverse events such as hypotension, nausea, vomiting, abdominal pain, oedema and metallic taste².

Hutchinson *et al.*³ and Dresow *et al.*⁴ have shown that giving oral iron therapy with ferrous salts, at dosages of only 60-100mg iron per dose, leads to transferrin saturation of up to 80% with resultant NTBI at each administration. They also observed similar side effects to those seen in the Chandler study. The most common side-effects associated with oral iron therapy (according to the Summaries of Product Characteristics) include: epigastric pain, indigestion, nausea, vomiting, diarrhoea, constipation, perforation of duodenal or jejunal diverticulum, urticaria, rash, exanthema and anaphylaxis⁵.

Table 1 shows the properties of various iron preparations. The tolerability of iron compounds

depends not only on the reactivity of the iron and how easily it is released from the carbohydrate but also on the size of the iron-carbohydrate complex and the nature of the carbohydrate moiety. The release rate of iron from polynuclear iron hydroxide-carbohydrate complexes is inversely related to the molecular weight of the complex¹ (Fig. 4).

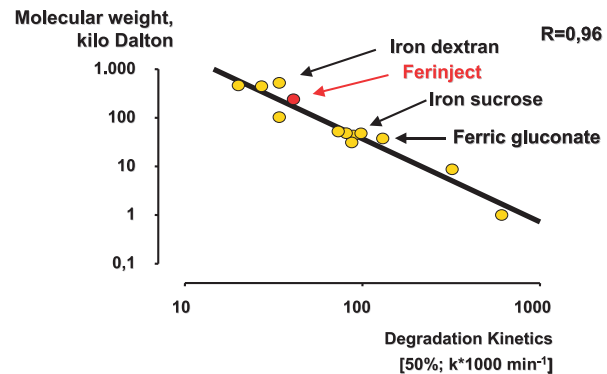


Figure 4

Iron release rate versus molecular weight of different iron-carbohydrate complexes showing an inverse relationship (modified from Geisser *et al.*¹)

Table 1

Classification of iron complexes

	Type I	Type II	Type III	Type IV
Example	Iron dextran BP/USP Iron dextrin	Iron sucrose	Iron (III)-gluconate Iron (III)-citrate Iron (III)-sorbitol	Iron (III)-citrate + iron (III)-sorbitol + iron dextrin Iron (III)-gluconate + iron sucrose
Preparations	Ferinject® InFeD® Dexferrum®	Venofer® Fesin®		Jectofer® Ferrelecit®
Characteristic	Robust and strong	Semi-robust and moderately strong	Labile and weak	Mixtures containing at least 2 different iron complexes
Molecular mass [Dalton]	>100,000	30,000-100,000	<50,000	<50,000
Reactivity				
degradation kinetics $k \cdot 10^3 \cdot \text{min}^{-1}$ at $\theta = 0.5$	15-50	50-100	>100	>100
with transferrin [$\mu\text{g iron/dL}$]	52.7 a	140.7 c		251.7 d
redox-active iron [μM]	0.57 b	1.11 c		1.52 d
redox potential [mV]	-475 a -390f	-526 c		-200 d
Toxicity				
*LD ₅₀	1013 a,e	359 c	not available	155 d
Oral	>2500	>2500	429-1000	
Intravenous	>2500	>200	13-16.5	

BP = British Pharmacopoeia, USP = US Pharmacopoeia, a = iron dextran, b = iron dextrin, c = Venofer®, d = Ferrelecit®, e = Martin *et al.*¹³, f = Ferinject®, * = LD₅₀ in white mice in mg Fe/kg body weight.

These characteristics will influence the clinical behaviour of the preparations.

In terms of the rate of elimination of the complex from the serum, FCM is intermediate between iron sucrose (which is eliminated more rapidly) and iron dextran (which is eliminated more slowly) (Fig. 5). The half-lives are 5 hours for iron sucrose, 16 hours for FCM and over 3 days for iron dextran (at a dose of 20mg iron/kg body weight).

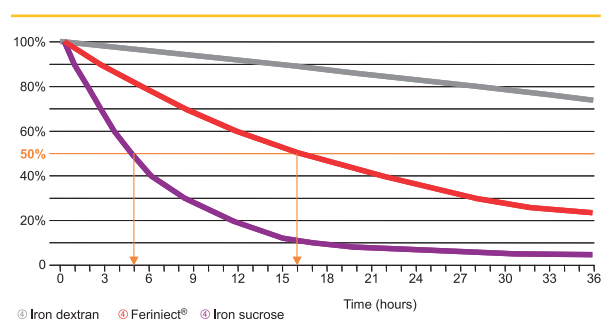


Figure 5

Serum elimination of FCM, iron dextran and iron sucrose in humans. Half life values from Crichton *et al.*⁸.

The rate of iron release is reflected in the side-effect profile, with more reactive compounds being less well tolerated. However, iron dextran (which has a low reactivity) has a higher incidence of side effects due to dextran-induced anaphylactic reactions⁶. Unlike iron dextran and iron gluconate, no fatalities have been reported with iron sucrose administration and the reported number of adverse events (per million dose equivalents) is lower⁷.

Ionic iron, especially the hydrated form of ferrous iron, Fe^{2+} and ferric hydroxide $\text{Fe}(\text{OH})_3$, can contribute to the processes that lead to the formation of free and latent hydroxyl radicals⁸. Fe^{2+} can enter the body from medicinal oral iron preparations but it is also possible that Fe^{3+} compounds react with superoxide or NADPH to form Fe^{2+} , depending on the reduction potential (Fig. 6).

Moreover, the reactivity of superoxide with fully saturated transferrin is greater than that with partially saturated transferrin⁹. This means that the pattern of transferrin saturation described above is responsible for oxidative stress, which may be considered a 'silent' side effect of iron therapy. The

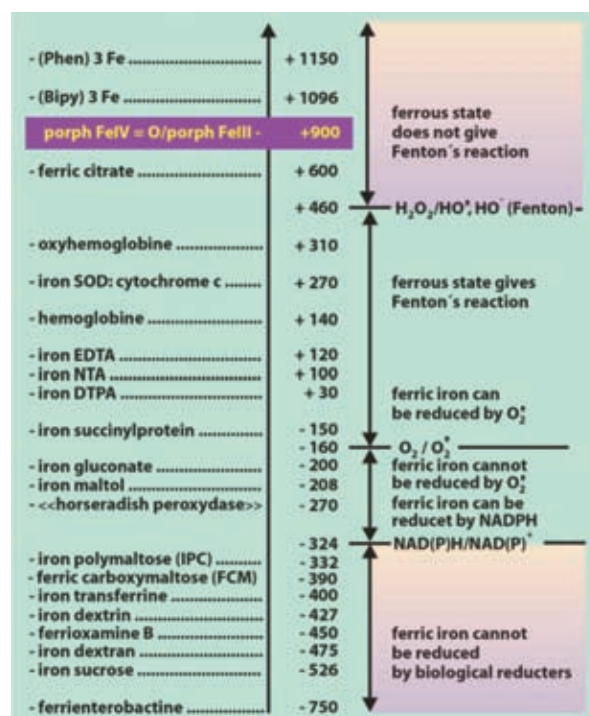


Figure 6

Reduction potentials of iron(III) compounds at pH 7.0 and the corresponding reactions (Crichton *et al.*⁸).

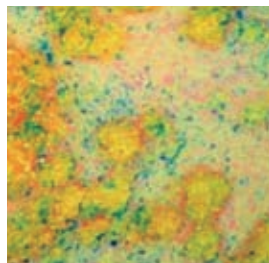
reduction potential of FCM is -390 mV, which prevents reduction to Fe^{2+} species.

PRECLINICAL STUDIES

Histological studies using a total dose of 200mg iron/kg body weight have confirmed that the iron is deposited in the RES and not in the parenchyma and therefore does not induce oxidative stress reactions. In contrast to iron gluconate, high dose FCM did not induce necrosis in mouse liver (Fig. 7). There was also no effect on aspartate amino transferase (AST), alanine amino transferase (ALT) or alkaline phosphatase following intravenous administration, in contrast to other preparations such as iron dextran and iron gluconate which caused increases in these liver enzymes¹⁰.

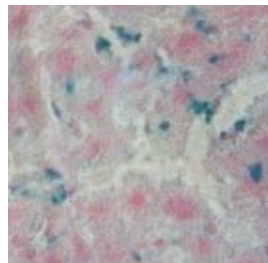
Long-term lack of oxidative stress associated with FCM is indicated by a number of parameters including the glutathione ratio and catalase activity in hepatic, cardiac and renal tissues four weeks after

Liver histotoxicity: microscopic pictures of mouse liver 4 hours after injection



Iron gluconate¹

Typical medium-sized and large necroses



FCM

No necroses

Geisser et al.¹

Figure 7

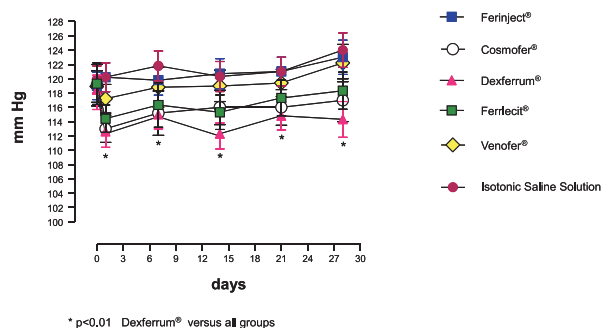
Histopathology: effects of intravenous iron gluconate and FCM on mouse liver (micrographs taken 4 hours after injection). Note the typical medium-to-large necrotic areas induced by iron gluconate compared with the lack of necrosis with FCM.

weekly i.v. iron administration. In contrast, iron gluconate causes increased lipoperoxidation by thiobarbituric reactive species (TBARS) and increased glutathione peroxidase concentrations. Iron gluconate and iron dextran cause significant decreases in the glutathione ratio (GSH/GSSG). However, in all these tests, there was no difference between FCM and isotonic saline¹⁰. These all suggest that FCM is less likely to cause oxidative stress than other iron compounds.

Preclinical studies with Ferinject® confirm the safety and tolerability predicted from the chemical properties of the complex. While Dextran causes a statistically significant decrease in systolic blood pressure, the effects of FCM could not be distinguished from those of isotonic saline (Fig 8). Rapid administration of high doses (240 mg Fe/kg bw in 2 seconds) to mice produced no changes in vital signs. Repeated dose studies in rats and dogs showed no adverse effects at a dose of 117 mg Fe/kg in both species. The highest non-lethal dose of FCM was found to be at least 5-times higher than that for iron sucrose [Vifor, data on file].

Preclinical tests show that FCM does not cross-react with dextran antibodies [Vifor, data on file].

FCM has no mutagenic potential, does not damage chromosomes and is not associated with bone marrow cell toxicity [Vifor, data on file]. At high doses (corresponding to between 1.2x and 12x the human



* p<0.01 Dextran® versus all groups

Figure 8

Effects of various iron-carbohydrate preparations on systolic blood pressure in rats. (Tobli¹⁰)

overdose level) there were no signs of embryo-foetal or maternal toxicity in experimental animals; there was also no pre- or post-natal toxicity and no effects on fertility or embryonic development.

CLINICAL PHARMACOKINETICS

Pharmacokinetic studies show a dose-proportional elimination of FCM from the serum, showing no signs of saturation at doses of up to 1000mg iron per patient.

Radiolabelling studies in patients with iron-deficiency anaemia or renal anaemia have shown that the iron from FCM is distributed in the liver and spleen and taken up predominantly by the bone marrow from within 60 minutes after administration while levels in the liver and spleen fall steadily after about 30 minutes. In all patients, the RBC utilisation increased rapidly up to days 6-9, then increased at a much slower rate (Fig. 9). Within 2-3 weeks of FCM administration, iron utilisation rates were 91-99% in the iron-deficient patients, and 61-84% in the patients with functional iron deficiency¹¹.

Repeat dose pharmacokinetic studies giving 500 or 1000mg iron as FCM weekly for 4 weeks showed no signs of saturation with multiple doses. This means that the elimination curve for repeated doses was the same as with a single dose^{8,12} (Fig. 10).

Use of FCM offers potential savings in terms of administration time and considerable advantages to patients compared to other intravenous iron preparations.

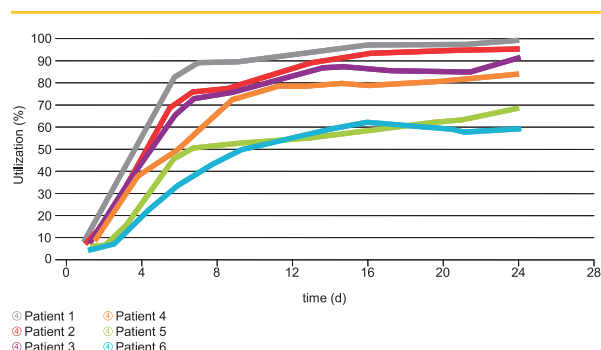


Figure 9

Red cell utilisation of $^{52}\text{Fe}/^{59}\text{Fe}$ labelled ferric carboxymaltose following a single i.v. administration in patients with iron deficiency, renal anemia or functional iron deficiency (modified from Beshara *et al.*¹¹)

A dose of up to 1000 mg iron may be given in 15 minutes. This compares with a maximum dose of 500 mg iron as iron sucrose which requires a 3.5 hour infusion following a test dose, or a 6-hour infusion and test dose for iron dextran.

In conclusion, FCM offers convenient administration and permits high doses of iron to be given in a short period. FCM also offers considerable benefits in terms of safety and tolerability compared with iron gluconate and iron dextran. This is due to the fact that FCM does not cross-react with dextran antibodies, is a highly stable complex, does not release ionic iron under physiological conditions, and does not provoke oxidative stress reactions.

Conflict of interest statement. Peter Geisser PhD is Scientific Director of Vifor (International) Ltd.

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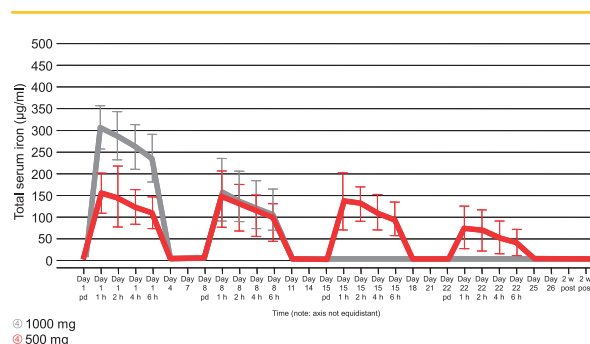


Figure 10

Mean total serum iron over time after weekly administration of 500 or 1000 mg iron as FCM showing identical elimination curves following repeated doses (from Rumyantsev *et al.*¹², in Crichton⁸)

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