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Pharmacokinetics of ferric bepectate—a new intravenous iron drug for treating iron deficiency

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Abstract

IV iron is indicated in clinical conditions, where rapid anaemia alleviation and repletion of iron stores are required. The acute toxicity of IV iron is ascribed to the presence of labile iron in plasma. Thus, shorter plasma residence time might improve the safety profile, even for compounds holding-on the iron tightly. In this single-centre, open-label, single-dose escalation study, we evaluated the elimination kinetics of ferric bepectate (FBP) compared to those of ferric carboxymaltose (FCM). Thirty-three iron-depleted anaemic patients who had undergone cardiac surgery were included and received 200, 500 or 1500 mg FBP or 500 mg FCM. Plasma drug curves were subjected to model-free analysis. Because saturation kinetics was found, a compartmental model with limited elimination capacity was applied. Urinary iron excretion was also analysed. The initial non-compartmental analysis revealed an increasing AUC/dose ratio for FBP. For both drugs, the central distribution compartment corresponded to plasma volume, and elimination followed Michaelis-Menten saturation kinetics. Maximal elimination rates (V_{max}) were 224 mg/h and 81 mg/h for FBP 500 mg and FCM 500 mg, respectively; drug concentrations at half V_{max} (K_m), 99 mg/L and 212 mg/L, respectively; and terminal plasma half-life (T½), 3.05 h and 8.96 h, respectively. Both drugs were equally effective in eliciting an early ferritin rise. Urinary iron excretion was measurable in all patients receiving FCM but not in those receiving FBP, which was well tolerated. Intravenous iron drugs are subject to capacity-limited elimination with different saturation thresholds. Urinary iron excretion can be used as a surrogate for labile plasma iron.

KEYWORDS

intravenous iron drugs, labile iron, michaelis-menten kinetics, side effects, urinary iron

1 | INTRODUCTION

Iron deficiency (ID) and iron deficiency anaemia (IDA) are highly prevalent worldwide.[1] The symptoms associated with IDA include fatigue, palpitations, dyspnoea, headache, lack of concentration, dizziness, leg cramps, insomnia and pica.[2] Treatment of IDA has been shown to improve energy, activity, quality of life (QOL), work capacity, cardiac function,

sexual function, cognition and outcome in a variety of clinical settings.[3-7]

Oral iron is generally accepted as the treatment of choice for the majority of patients due to ease of administration, low cost and perceived effectiveness, but the incidence of side effects is considerable, thus, limiting adherence with long-term therapy.[8,9] A recent Cochrane Review raised doubts regarding the therapeutic value of oral iron for correcting postpartum anaemia.[10] In addition, recent evidence reports that the ingestion of oral iron raises hepcidin levels, which are maintained for more than 24 h, thus, reducing absorption of the next daily dose.[11,12]

Intravenously (IV) administered carbohydrate-coated iron nanoparticles are taken up by the reticuloendothelial system and broken down within the lysosomes. The iron is subsequently transferred to the cytoplasm and stored into ferritin or exported back to the plasma, where it is bound to transferrin and transported to the bone marrow and other tissues for use in erythropoiesis and/or energy metabolism.[13] All IV iron formulations currently used in clinical practice contain varying amounts of labile iron (i.e. iron that is not tightly bound to the complex and can be released into plasma after administration), with the highest levels being reported in iron sucrose and the lowest in ferric bepectate (FBP).[14,15] Labile iron can be released into plasma and lead to transferrin oversaturation, and non-transferrin bound iron, depending on the compound and the administered dose.[13,14] IV iron therapy has been shown to restore haemoglobin levels faster than oral iron,[16] and in several surgical settings where post-operative anaemia is frequent, IV iron improved the patient-related outcome compared to oral iron or no treatment.[17,18]

The acute toxicity of IV iron is ascribed to the presence of labile iron in plasma (LPI), hypersensitivity to the carbohydrate moiety of the iron complex (IgE-mediated) or complement activation by iron nanoparticles.[19] Non-transferrin bound iron (NTBI) and its redox active LPI component are thought to be potentially toxic forms of iron, promoting the formation of highly reactive free radicals such as the hydroxyl radical, which targets endothelial cells, the myocardium, the liver and low-density lipoprotein.[20]

In normal human urine, only minute concentrations of iron are found; however, higher concentrations of urinary iron have been detected after IV iron administration,[21,22] even though the molecular weight and hydrodynamic diameter (d_H) of the iron drug complexes are above the glomerular filtration threshold (<10 nm).[14,15,23,24]

FBP is a newer IV iron formulation in which the iron core is coated with a hydroxyethyl-amylopectin derivative. This single-centre, open-label, single-dose escalation study aimed to evaluate the elimination kinetics of FBP (200-1500 mg IV) and to monitor its safety, as judged by urinary iron excretion. A comparison with a currently marketed IV iron drug (ferric carboxymaltose [FCM], 500 mg) was also performed.

2 | PATIENTS AND METHODS

2.1 | Ethics

The trial was conducted at Copenhagen University Hospital (Rigshospitalet) according to the Good Clinical Practice Guideline, Research Ethics Committee regulations and applicable government regulations. The protocol, amendments, informed consent form and subject information form were reviewed and approved by the Danish Medicines Agency (Lægemiddelstyrelsen) and by the local Independent Ethics Committee (De Videnskabsetiske Komitéer for Region Hovedstaden). All ethical and legal requirements were met before enrolment of the first patient. The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies.[25]

2.2 | Study design and patients

The clinical trial (EudraCT Number: 2015-003069-28) was a prospective, open-label, single-dose escalation pharmacokinetic study of FBP in the early post-operative phase of patients who had undergone heart surgery. This population was selected because low haemoglobin concentrations are required for high-dose pharmacokinetics and, according to our Ethic Committee, healthy volunteers should not receive high-dose IV iron infusions.

Patients were screened from November 2015 to October 2016 and enrolled after giving informed consent prior to cardiac surgery. When the post-operative bleeding ceased, they were re-evaluated to confirm that inclusion and exclusion criteria were met. The study duration was 5 days, and the post-dosing follow-up was 72 hours.

The study was conducted in a staggered design. The first cohort received 200 mg FBP. The second cohort was randomized to receive either 500 mg FBP or 500 mg FCM. The third cohort was administered 1500 mg FBP. All IV formulations were dosed over 15 minutes. as undiluted drug via an infusion pump.

2.2.1 | Inclusion criteria

Anaemic patients aged ≥18 years who provided signed informed consent, underwent cardiac surgery performed with mortality risk <6 according to EuroSCORE-II and had a systolic/diastolic blood pressure <145 mmHg/<95 mmHg were included. To avoid the use of a bladder catheter, only males were included to secure a valid urine collection.

To avoid overdosing, especially when administering 1500 mg FBP, required pre-infusion haemoglobin (Hb) levels were defined according to the Ganzoni's formula[26]:

$$\text{iron deficiency} = [\text{target Hb,g/dL} - \text{pre-infusion Hb,g/dL}] \times 2.4 \times \text{body-weight, kg}).$$

2.2.2 | Exclusion criteria

Patients were excluded if they met any of the following criteria: body-weight <50 kg; ongoing bleeding >50 mL/h for the 3 hours before the start of drug dosing; unexplained anaemia or non-iron deficiency anaemia; anticipated medical need for erythropoietin; known hypersensitivity to the investigational drugs; known drug allergy, immunological or inflammatory diseases, severe asthma, eczema or atopy; preoperative anaemia treatment within 3 months prior to screening; s-ferritin >800 ng/mL; imminent dialysis; infection (T > 38.5°C or subject on non-prophylactic antibiotics); chronic liver disease or screening alanine aminotransferase (ALAT) or aspartate aminotransferase (ASAT) three times above the upper limit of the normal range; renal disease defined as proteinuria and creatinine >150 µmol/L; primary haematologic disease; known malignant disease/cancer within the last 5 years; insulin-treated diabetes; history (current or past) of drug or alcohol abuse; known or suspected inability to comply with the trial protocol (e.g. due to psychological disorders or other conditions); receipt of any investigational medicinal products within the previous 90 days. Patients were also excluded if they received any perioperative blood transfusion during the study period.

2.3 | Objective and outcome measures

The primary objective was to assess the dose linearity pharmacokinetics of FBP at doses of 200 mg, 500 mg or 1500 mg infused intravenously over 15 minutes, with respect to area under the curve (AUC) and maximum serum concentration (C_{max}). Further kinetic analyses were performed to characterize volumes of distribution (V_c, V_p), maximal rate of disappearance from plasma (V_{max}) and concentration (K_m) at half V_{max}. The secondary objective was to compare FBP with FCM, both at a dose of 500 mg, regarding pharmacokinetics, early urinary iron excretion, short-term effects on transferrin saturation (TSAT) and s-ferritin, and general safety of FBP administration.

2.4 | Blood and urine samples and laboratory determinations

Baseline blood samples were obtained in 9 mL lithium heparin tubes. After the start of IV iron dosing, blood samples were drawn at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 24, 48 and 72 hours. Urine samples were obtained from urine collected between 0-8, 8-24, 24-48 and 48-72 hours post-dosing. Haemoglobin, TSAT, serum iron, transferrin and ferritin were determined at baseline and at 8, 24, 48 and 72 hours (efficacy variables). Iron in plasma and urine samples was analysed by Eurofins (a GLP- and ISO17025-accredited laboratory; Glostrup, Copenhagen) by inductively coupled plasma atomic emission. The lower limit of quantification (LLQ) was 0.5 µg/mL and 0.1 µg/mL for serum and urine iron, respectively. The analytical method has been validated according to the EMA guidelines on bioanalytical method validation [EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**, 21 July 2011].

2.5 | Clinical safety

The clinical safety evaluation included adverse events, coded by system organ class and preferred term using the latest Medical Drug Dictionary for Regulatory Activities version 15.1 [https://www.meddra.org]. These events were recorded and evaluated for relatedness to the investigational product, seriousness, severity and expectedness.

2.6 | Kinetic analysis

The initial kinetic analysis used a non-compartmental model with a WinNonlin methodology programmed in SAS by backward analysis of the terminal plasma iron versus time curves, corrected for baseline plasma iron level, to calculate terminal rate constant. The AUC was calculated using the trapezoidal rule from zero time and extrapolated to time infinity by integration using the calculated rate constant.

As the non-compartmental kinetic analysis indicated saturation kinetics, a compartmental pharmacokinetic analysis was employed with a capacity-limited elimination from the primary volume of distribution, and a 2-compartment model with the following constants was preferred: central volume of distribution (V_c), peripheral volume of distribution (V_p), rate constants for transferral between V_c and V_p (k_{cp} and k_{pc}), and output from V_c according to the formula:

$$dC/dt = [A(t)/V_c] \cdot V_{max}/[K_m + [A(t)/V_c]]$$

(Michaelis-Menten equation, where $A(t)$ is the amount of iron at time t).

A non-linear iterative curve fitting was performed in ADAPT-5, with the iterative naïve pooled data maximum likelihood procedure,[27] on the individual plasma concentrations versus time; the FBP 200 mg and 500 mg data were analysed in one cohort, as the kinetic appeared identical and the estimation of the kinetic parameters improved. To prevent the influence of a shift in baseline plasma iron, only samples from 0 to 8 hours for the FBP groups and from 0 to 24 hours for the FCM group were included.

2.7 | Statistics

No formal sample size calculation was performed. The primary and secondary analyses were conducted on the per-protocol population, which comprised all patients who received

the trial drug and did not have any major protocol deviations. All continuous variables were summarized using descriptive statistics by treatment group. The categorical variables were summarized with counts and percentages. The safety analysis was conducted on the safety population, which comprised all patients who received the drug.

3 | RESULTS

Overall, 79 patients were screened for inclusion in the trial; the number screened for FBP 1500 mg administration was high, as only 8 out of 54 presented with the adequate Hb level for inclusion. Two FBP patients withdrew their consent: one prior to drug dosing and one during follow-up (8 hours after dosing). For the latter, data obtained until withdrawal of consent were included in all analyses. One protocol violation occurred regarding one patient who received 500 mg FBP despite a high ferritin level. Data from this patient were included in the pharmacokinetic analysis but excluded from the pharmacodynamic analysis. Two patients in the FBP 1500 mg group were judged as protocol violators, as the calculated plasma volume based on the 15-min. plasma iron level was inconsistent with human physiology. These patients were included in the safety analysis and were excluded from the population kinetic analysis. Patient demographics and baseline characteristics are summarized in Table 1.

3.1 | Kinetic analysis

Data from the initial non-compartmental analysis performed are summarized in Table 2. Interestingly, $T_{1/2}$ was significantly shorter for FBP (1.68-3.05 hours) than for FCM (8.96 hours). The AUC/dose ratios for increasing FBP dosage were found to differ significantly from unity; thus, dose-dependent kinetics was proven. This finding initiated a further pharmacokinetic analysis in which capacity-limited elimination was included.

The kinetic analysis was supplemented by a naïve pooled kinetic analysis of the plasma drug disappearance curves using both a one-compartment and a two-compartment model with capacity-limited elimination. The two-compartment model was found to be superior to the one-compartment model. The observed and estimated curves for plasma iron at different FBP dosages are depicted in Figure 1A.

The mean population kinetic results for FBP and FCM are summarized in Table 3. The V_{max} values were 224 mg/h, 231 mg/h and 81 mg/h for FBP 200-500, FBP 1500 and FCM 500, respectively, whereas the K_m values were 99 µg/mL, 40 µg/mL and 212 µg/mL, respectively. V_c corresponded

TABLE 1 Demographics and baseline characteristics

	Ferric bepectate			Ferric carboxymaltose
Dose	**200 mg**	**500 mg**	**1500 mg**	**500 mg**
Analysis set, n	8	9	6	8 (100)
Age (years)	70 (9)	67 (10)	61 (12)	67 (7)
Race (White/Asian/Other)	8/0/0	9/0/0	5/1/0	8/0/0
Height (cm)	177 (4)	177 (3)	184 (8)	178 (4)
Weight (kg)	85 (14)	85(12)	96 (12)	91 (20)
Body surface area (m^2)	2.01(0.13)	2.02(0.12)	2.19(0.1)	2.08(0.20)
Estimated blood volume (L)[a]	5.36 (0.45)	5.39 (0.41)	6.00 (0.54)	5.61 (0.67)
Estimated plasma volume (L)[b]	3.76 (0.39)	3.61 (0.43)	4.29 (0.39)[c]	3.67 (0.31)
Haemoglobin (g/dL)	9.98 (0.98)	11.04 (1.32)	9.18 (0.56)[c]	11.41 (0.45)
s-Ferritin (ng/mL)	259 (98)	333 (335)	329 (194)	334 (100)
s-Iron (µg/dL)	21 (6)	32 (22)	28 (25)	31 (16)
TSAT (%)	8.3 (3.6)	9.1 (3.3)	7.0 (1.0)	9.9 (3.9)

Notes: All data are presented as the mean (standard deviation) or number (%). Baseline values were obtained after surgery and before IV iron administration. No statistically significant differences were found between the polyglucoferron 500 mg group and the ferric carboxymaltose 500 mg group ($P > 0.05$).

[a]Nadler's formula: Blood volume (L) = (0.3669 × Height^3 [m^3] + (0.03219 × Weight [kg]) + 0.6041 (Males).

[b]According to estimated blood volume and haematocrit.

[c]$P < 0.01$, with respect to other groups (Kruskal-Wallis test).

[Correction added on 14 May 2019, after first online publication: Table 1 has been updated in this version].

TABLE 2 Non-compartmental pharmacokinetic parameters

	Ferric bepectate			Ferric carboxymaltose
	200 mg (mean, CV%)	500 mg (mean, CV%)	1500 mg (mean, CV%)	500 mg (mean, CV%)
AUC, μg[a]h/mL	115 (21)[a]	432 (30)[a]	1669 (51)[a]	1923 (23)
Cmax, μg/mL	62 (17)	150 (19)	383 (28)	129 (14)
AUC[a]/Dose, h/L	48 (23)	73 (27)	106 (51)	348 (30)
$Lambda_z$ /h	0.47(50)	0.37 (66)	0.43 (119)	0.08 (12)
T/2, h	1.68 (29)	3.05 (69)	2.85 (51)	8.96 (12)
CL, L/h	1.83 (26)	1.26 (30)	1.08 (38)	0.28 (26)
V_z, L	4.2 (22)	4.78 (58)	4.21 (75)	3.57 (32)

Notes. AUC denotes the area under the curve time 0 to infinity; Cmax, maximal observed plasma concentration; Lambda, terminal rate constant; T/2 terminal half-life; CL, clearance; V_z, apparent volume of distribution.
[a]Significantly different increments corrected for dose, $P < 0.05$,

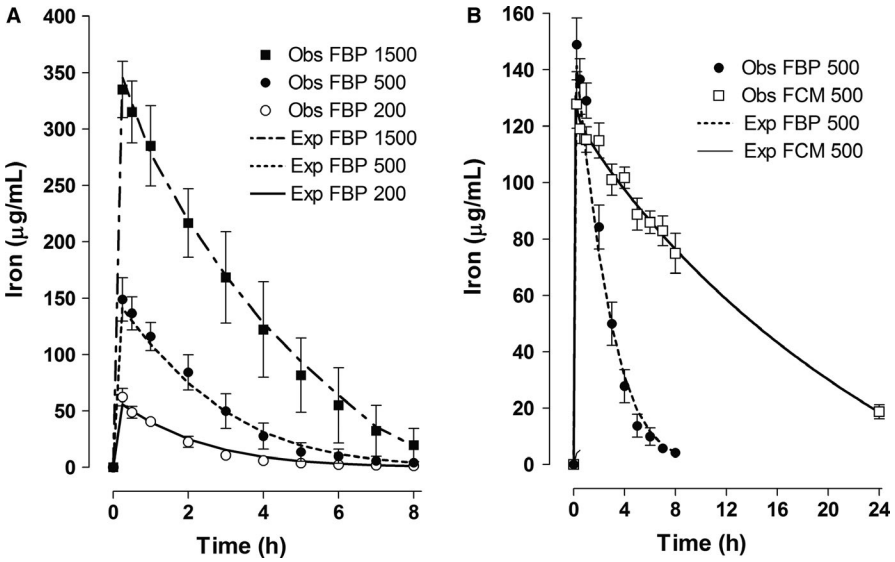

FIGURE 1 A, Expected (lines) and observed (mean ± *SEM*) time course of iron concentrations after intravenous dosing of 200 mg (○), 500 mg (●) or 1500 mg (■) ferric bepectate (FBP). B, Expected (lines) and observed (mean ± *SEM*) time course of iron concentrations after intravenous dosing of 500 mg ferric bepectate (FBP, ●) or ferric carboxymaltose (FCM, □)

to the assumed plasma volume (2.9 L, 3.4 L and 3.1 L, respectively), and V_p values were smaller (0.15 L, 0.67 L and 0.96 L, respectively), though a wide coefficient of variation was observed in V_p for FBP 200-500.

3.2 | Early iron parameters

The observed s-iron concentrations measured by standard clinical chemical methods and the corresponding TSAT values are depicted in Figure 2. The increase in s-iron was significantly higher in the FCM 500 mg group than in any FBP group (Figure 2A). Additionally, "apparent" TSAT was significantly higher for FCM despite the dose being only 33% of the highest FBP dose. For both formulations, TSAT values at 72 hours post-infusion tended to be higher than those at pre-infusion. Moreover, at 72 hours post-infusion, there was a trend towards higher TSAT values in the FBP 500 mg group compared to those in the FCM 500 mg group (21 ± 10% vs 15 ± 3%, $P = 0.137$) (Figure 2B). As depicted in Figure 2C, a dose-dependent, but not dose-linear, fractional rise in s-ferritin concentrations was observed after all IV iron treatments. Moreover, increases in s-ferritin after IV administration of 500 mg FBP or FCM were almost identical (Figure 2C).

3.3 | Urinary iron excretion

One patient in the FBP 500 mg group had late positive urinary iron, and one in the FBP 1500 mg group had urinary iron levels above the LLQ in all samples (Table 4). In contrast, all patients in the FCM 500 mg group had urinary iron above the LLQ in the 0-8 hours post-dosing samples, five had positive urine iron in the 8-24 hours samples, and none were positive in the 24-48 hours and 48-72 hours samples (Table 4).

TABLE 3 Population pharmacokinetic parameters from ADAPT 5, Naïve pooled data (two-compartment model)

	Ferric bepectate 200 mg and 500 mg		Ferric bepectate 1500 mg		Ferric carboxymaltose	
	Estimate	%CV	Estimate	%CV	Estimate	%CV
K_m, mg/L	99.2	0.77	39.5	1.31	212	3.45
V_{max}, mg/rh	224	0.48	231	0.32	80.8	2.61
V_c, L	2.91	0.91	3.41	0.61	3.1	2.47
k_{cp}, /h	0.38	43.5	1.27	5.82	2.00	27.9
k_{pc}, /h	7.73	25.9	4.52	3.53	9.21	14.7
Cld, L/h	1.13	42.5	4.34	5.25	6.18	25.5
V_p, L	0.15	17.6	0.96	2.04	0.67	11.0
AIC - 2C	192873		114282		68021	
AIC - 1C	193127		117373		69008	
Prob for 1C	<0.001		<0.001		<0.001	

Note. %CV, coefficient of variation; K_m, Michaelis-Menten constant; V_{max}, estimated maximal rate of elimination; V_c, central volume of distribution; k_{cp}, k_{pc}, rate constants for transfer from central to peripheral volume of distribution and reverse; Cld, clearance between compartments; V_p, peripheral volume of distribution; AIC, Akaike information criterion; 1C and 2C, one- and two-compartment; Prob, probability.

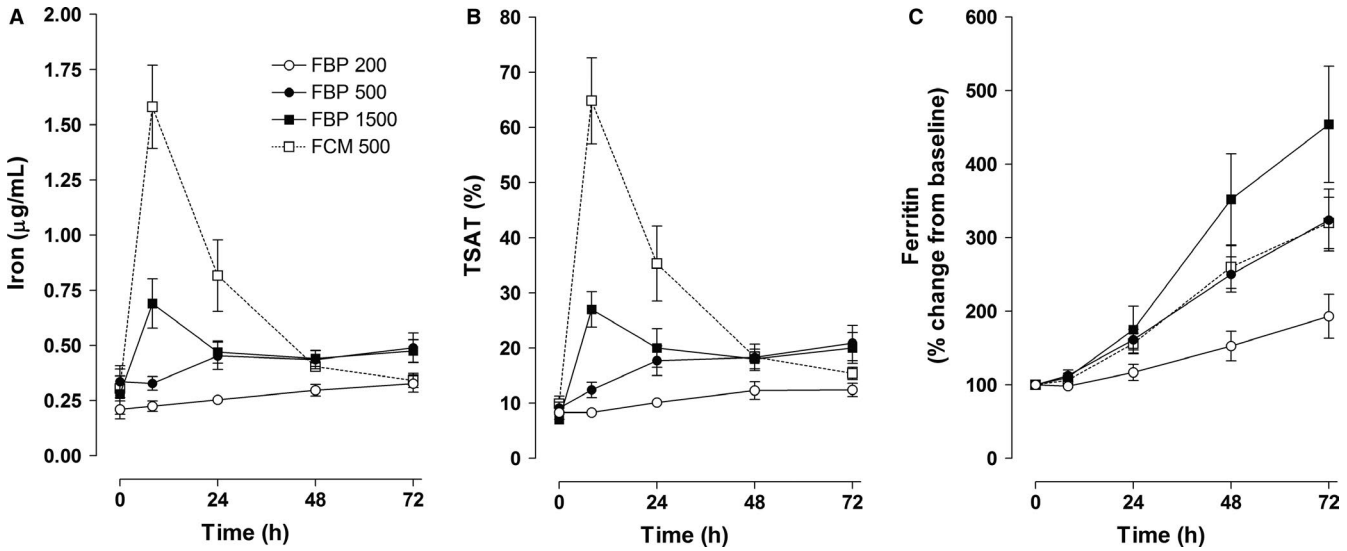

FIGURE 2 Time course of iron concentration (A), transferrin saturation index (B) and ferritin concentrations (C) after intravenous dosing of ferric bepectate (FBP) 200 mg (○), 500 mg (●) or 1500 mg (■), or ferric carboxymaltose (FCM) 500 mg (□). Data are presented as the mean ± *SEM*

3.4 | Safety

Both drugs were well tolerated. No major adverse events were observed, though one patient in the FBP 1500 mg group reported pyrexia and another in the FBP 500 mg group showed an abnormally high ferritin level, with both rated as possibly drug-related.

4 | DISCUSSION

Few pharmacokinetic studies with highly clinically relevant doses of IV iron drugs are available, despite the clinical use of these drugs for more than fifty years. Several studies relied on a model-free analysis,[22,27,28] though a more sophisticated analysis has recently been introduced. Our main objective was to clarify whether FBP has a saturable elimination pathway, as previously found for iron dextran,[28] iron isomaltoside[29] and FCM.[30] The model-free analysis demonstrated a dose non-linear increase for AUC, which indicates saturable elimination kinetics.

We then supplemented the analysis using both one- and two-compartment models with a saturable elimination from the central compartment. As the study population was homogenous, except for the higher estimated plasma volume in the FBP 1500 mg group (Table 1), the possibility of revealing

TABLE 4 Urinary iron excretion after dosing with polyglucoferron or ferric carboxymaltose

Post-dosing urine sampling time	Ferric bepectate						Ferric carboxymaltose	
	200 mg		500 mg		1500 mg		500 mg	
	Urine volume (mL)	Positive samplesn/N	Urine volume (mL)	Positive samplesn/N	Urine volume (mL)	Positive samplesn/N	Urine volume (mL)	Positive samples n/N
0-8 h	941 (618)	0/8	865 (589)	0/9	967 (579)	1/6	830 (482)	8/8
8-24 h	1606 (667)	0/8	1798 (901)	0/9	1430 (555)	1/6	1375 (737)	5/8
24-48 h	2461 (268)	0/8	1583 (1046)	1/9	1858 (405)	1/6	1643 (373)	0/8
48-72 h	2118 (775)	0/8	2312 (804)	0/9	1683 (971)	1/6	2106 (901)	0/8

Notes. Positive sample defined by urinary iron concentration above the lower limit of detection (0.1 µg/mL).
Values are mean ± *SD* or incidence/total number.

covariates based on patient characteristics was non-existent because the included patients were homogenous; thus, we used the naïve pooled method to estimate pharmacokinetic variables for all patients receiving the respective drugs.[31] The preliminary kinetic analysis showed almost identical results in the two FBP lower dose groups, while a secondary volume of distribution increased in the high-dose group. For FCM and FBP, the best fit was obtained with a two-compartment model; this model was previously used for the high-molecular weight formulation ferumoxytol (>150 kD).[32] The V_c was found to correspond with the assumed plasma volume, which was expected, as the drugs should be restricted to the plasma. A smaller V_p was found for FCM 500 mg and FBP 1500 mg, suggesting that when given at high doses, some iron-carbohydrate macromolecules can temporarily leave the plasma and re-enter later as intact complexes. Sinusoidal capillaries in the liver are fenestrated (50-180 nm) and lined with Kupffer cells, which rapidly uptake large nanoparticles (d_H > 100 nm).[24] Smaller nanoparticles, such as FBP or FCM, may be trapped in the Disse space, where they can be taken up by hepatocytes or return to circulation as intact iron-carbohydrate complexes.[24]

The calculated V_{max} for FBP was considerably higher than that found for FCM (Table 3) or iron isomaltoside,[22,30] and this characteristic was also reflected in their respective terminal half-lives (Table 2). Further, the K_m for FBP was also lower, indicating a higher affinity for cellular uptake. Thus, systemic exposure to the carbohydrate-iron complex is shorter for FBP than for FCM, ferumoxytol and iron isomaltoside.[22,29,30,32] This finding indicates a faster uptake of FBP by the reticuloendothelial system, similar to that of USPIOs for which the plasma half-life is inversely correlated to particle size.[33] The estimated particle size of FBP is larger than 1000 kD, significantly greater than the estimated size of FCM (150 kD), ferumoxytol (750 kD) and iron isomaltoside (150 kD).[14,15]

LPI represents a health hazard, as it may cause oxidative stress and even direct vascular damage.[34] Methods for estimating NTBI and LPI are commercially available, though there is a need for thorough method validation protocols and standardization.[35] However, in patients with iron-overload disorders, increased TSAT, but not ferritin, was a good indicator of the presence of forms of circulating NTBI, with a threshold of approximately 70%.[35] As depicted in Figure 2B, no sign of transferrin oversaturation was observed for any FBP dose at any time during the 72-hr follow-up, while "apparently" high TSAT levels were observed in samples drawn 8 hours after 500 mg FCM dosing (65 ± 8%). However, traditional methods for estimating TSAT assume that all serum iron is bound to transferrin and, therefore, may lead to gross overestimation of TSAT following administration of IV iron formulations.[36]

Urinary iron excretion monitoring, early after IV iron dosage when plasma concentration of the IV iron complex is

high, could be a surrogate marker for the presence of NTBI or LPI in plasma, as d_H of the tested IV iron drugs (27.5 nm for FCM; 63.3 nm for FBP)[14,15] and molecular weight of transferrin (≈80 kD) are considerably higher than the glomerular filtration threshold.[23,24] Nevertheless, transferrin leakage (due to glomerular damage), increased plasma-free haemoglobin or haem (due to intravascular haemolysis) or microscopic lower urinary tract bleeding can also increase urine iron content and should be excluded.[37]

Virtually, no iron was found in urine in the early hours after FBP dosing, whereas most patients receiving FCM had positive urinary iron excretion during the first 24 hours post-dosing (Table 4). However, as urinary output in this patient population was high, excreted iron might have been diluted to concentrations below the LLQ, thus leading to infra-estimation of iron elimination in urine. In fact, estimated urinary iron excretion after FCM infusion was approximately 0.1%-0.2% of the administered dose, which is in accordance with published values.[28,37] Higher urinary excretion has been reported for iron isomaltoside (0.9%-1.1% for 100-200 mg),[22] ferric gluconate (2.4%-2.3% for 62.5-125 mg)[38] or iron sucrose (5% for 100 mg after 4 hours).[39] These data seem to further support the very low labile iron content of the FBP carbohydrate-iron complex, previously demonstrated by *in vitro* methods.[14,15]

Regarding early pharmacodynamics, the shorter plasma half-life can explain the lower "apparent" TSAT levels observed after all FBP doses (200-1500 mg) compared to that after FCM (500 mg) (Figure 2B). According to estimated half-life for BFP and FCM (Table 2), at 72 hours after infusion, virtually, all carbohydrate-iron complexes should have been removed from the circulation, thus minimally interfering with standard TSAT calculation, which showed a trend to higher values compared to pre-infusion ones (Figure 2B). At this post-infusion time, a trend towards higher TSAT values for FBP 500 mg compared to FCM 500 mg (21 ± 10% vs. 15 ± 3%, $P = 0.137$) was also observed (Figure 2B). Overall, these results suggest similar bioavailability of the iron contained in both iron-carbohydrate complexes.

Serum ferritin is an indirect measurement of iron stores, but it is also an acute phase reactant and its levels can rise in response to inflammation.[36] To correct for the effects of the post-operative inflammatory response, post-infusion s-ferritin increases during the 72-hours follow-up were expressed as the percentage of the pre-dosing level and non-linear, dose-dependent increases were found. This early effect of IV iron administration on s-ferritin has been previously documented for FCM.[30,40] Interestingly, s-ferritin increases after the administration of FBP 500 mg or FCM 500 mg were almost identical (Figure 2C), suggesting that both drugs were effectively taken up by cells from the reticuloendothelial system, where the iron is released from the complex to be transiently stored as ferritin, and then exported from the cells into the plasma where is taken up by transferrin.[21]

Neither serious adverse events nor clinically relevant changes in safety variables were observed in patients receiving FBP or FCM.

In summary, FBP has the lower labile iron content and the shorter plasma half-life, compared with any other high-molecular weight IV iron drug. This could represent a therapeutic advantage, especially in situations where administration of a single, high IV iron dose is preferred. Whether the risk of oxidative stress could be lower and of shorter duration with FBP than with other IV iron compounds deserves further investigation.

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CONFLICTS OF INTEREST

SW is employed by Iron4u. SM is employed by Serumwerk Bernburg AG. MM has received industry-supplied funding for consultancies, lectures and/or travel from Iron4u, Pharmacosmos, Vifor Pharma, Zambon and PharmaNutra. TS and PSO have nothing to disclose.

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