Pharmacokinetics of Ferric Pyrophosphate Citrate, a Novel Iron Salt, Administered Intravenously to Healthy Volunteers

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Abstract

Ferric pyrophosphate citrate (Triferic) is a water-soluble iron salt that is administered via dialysate to maintain iron balance and hemoglobin in hemodialysis patients. This double-blind, randomized, placebo-controlled, single-, ascending-dose study was conducted to evaluate the pharmacokinetics and safety of intravenous ferric pyrophosphate citrate in 48 healthy iron-replete subjects (drug, n = 36; placebo, n = 12). Single doses of 2.5, 5.0, 7.5, or 10 mg of ferric pyrophosphate citrate or placebo were administered over 4 hours, and single doses of 15 or 20 mg of ferric pyrophosphate citrate or placebo were administered over 12 hours via intravenous infusion. Serum total iron (sFe_{tot}), transferrin-bound iron (TBI), hepcidin-25, and biomarkers of oxidative stress and inflammation were determined using validated assays. Marked diurnal variation in sFe_{tot} was observed in placebo-treated subjects. Concentrations of sFe_{tot} and TBI increased rapidly after drug administration, with maximum serum concentrations (C_{max}) reached at the end of infusion. Increases in baseline-corrected C_{max} and area under the concentration-time curve from 0 to the time of the last quantifiable concentration (AUC_{0-t}) were dose proportional up to 100% transferrin saturation. Iron was rapidly cleared (apparent terminal phase half-life 1.2-2 hours). No significant changes from baseline in serum hepcidin-25 concentration were observed at end of infusion for any dose. Biomarkers of oxidative stress and inflammation were unaffected. Intravenous doses of ferric pyrophosphate citrate were well tolerated. These results demonstrate that intravenous ferric pyrophosphate citrate is rapidly bound to transferrin and cleared from the circulation without increasing serum hepcidin levels or biomarkers of oxidative stress or inflammation.

Keywords

ferric pyrophosphate citrate, intravenous, iron, hepcidin, pharmacokinetics

Iron deficiency is a common cause of anemia in patients with stage 5 hemodialysis-dependent chronic kidney disease (CKD-5HD). Erythropoiesis-stimulating agents and iron are essential components for the management of anemia in these patients. Erythropoiesis-stimulating agents increase the numbers of erythroblasts, whereas iron is needed in the final synthesis of hemoglobin to produce fully functional red blood cells (RBCs).

All currently available intravenous iron products are iron-carbohydrate complexes. The iron is bound to the carbohydrate shell and requires metabolism in the reticuloendothelial system (RES) via the RBC salvage pathway to export ferrous iron that, after oxidation to ferric iron, is bound to circulating transferrin.[1] The concurrent systemic inflammation in patients with CKD-5HD results in elevation of hepcidin, which blocks absorption of iron across the enterocyte and impairs release of iron from the RES.[2] This results in ineffective utilization of intravenous iron and has contributed to the rise in ferritin levels that has been observed over the last 10 to 15 years with the increased use of intravenous iron as "maintenance" therapy for patients with CKD-5HD.[3–6] The safety profile of intravenous iron preparations is generally favorable, but to date, long-term studies are lacking. However, inflammation, tissue injury, anaphylaxis, endothelial dysfunction, and oxidative stress have been described with the use of intravenous iron.[6,7]

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Ferric pyrophosphate citrate (Triferic) is a novel complex iron salt that is water soluble and contains no carbohydrate shell. Ferric pyrophosphate citrate is approved in the United States as an iron-replacement treatment to maintain hemoglobin concentrations in patients with CKD-5HD. Ferric pyrophosphate citrate is added to the bicarbonate concentrate at each hemodialysis session. The bicarbonate concentrate with ferric pyrophosphate citrate iron subsequently mixes with acid concentrate and water in the hemodialysis machine to generate dialysate containing 2 μM (110 μg/L) of iron(III). Ferric pyrophosphate citrate crosses the dialyzer membrane, enters the blood, donates its iron directly to transferrin, and is rapidly cleared from the circulation.[8] This provides for iron utilization for erythropoiesis and avoids hepcidin-induced iron sequestration within reticuloendothelial macrophages.[9,10]

Patients who use hemodialysis systems that do not use liquid bicarbonate concentrate cannot receive ferric pyrophosphate citrate iron via the hemodialysate. The availability of ferric pyrophosphate citrate iron for administration by a route other than the hemodialysate can provide a suitable therapeutic option to the currently available intravenous iron preparations for these patients. Furthermore, patients who have anemia of inflammation and functional iron deficiency with high serum hepcidin concentrations are potential candidates for a parenteral iron product that can bypass reticuloendothelial processing.

Ferric pyrophosphate citrate is a form of protected iron in which citrate and pyrophosphate are tightly complexed to the iron. Ferric pyrophosphate citrate is highly soluble in aqueous solutions and, therefore, can be easily formulated for intravenous administration. This formulation would allow patients with CKD-5HD who are using solid bicarbonate cartridges for bicarbonate generation to receive ferric pyrophosphate citrate iron concurrently with hemodialysis. Because of its unique chemical properties, ferric pyrophosphate citrate may also be a suitable addition to total parenteral nutrition solutions containing amino acids and lipids.

We conducted the current study to investigate the pharmacokinetics of intravenously administered ferric pyrophosphate citrate iron in healthy iron-replete subjects. The effects of intravenously administered ferric pyrophosphate citrate iron on serum concentrations of soluble transferrin receptor (sTfR), hepcidin-25, and biomarkers of oxidative stress and inflammation were also examined.

Methods

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices guidelines. The study protocol and written informed consent statement were approved by an institutional review board (IntegReview IRB, Austin, Texas) before subjects were enrolled into the trial. Written informed consent was obtained from all subjects before any study-related procedures were performed. The study was registered at www.clinicaltrials.gov as NCT01920854.

Subjects

Healthy male and female subjects aged 18 to 55 years with a body mass index between 20.0 and 32.0 kg/m² and no clinically relevant abnormalities based on medical history, physical examination, vital sign measurements, electrocardiograms (ECGs), or safety laboratory tests were enrolled in the study. Female subjects were not pregnant or breastfeeding and were at least 9 months postpartum. Subjects agreed not to use iron preparations during the 14 days before administration of the test material and to use acceptable birth control measures for the duration of the study.

Subjects were excluded if they had a hemoglobin concentration of less than 11 g/dL, a hematocrit of less than 30%, or a serum iron concentration of less than 70 μg/dL (male or female) at screening; had taken prescription medications (except hormonal replacement, hormonal oral contraceptives, acetaminophen, or antiinflammatory drugs) within 14 days before administration of the test material; currently used tobacco or other nicotine-containing products; or had a history of alcohol or other substance abuse within the past year or evidence of ethanol or drugs of abuse on baseline toxicology screens. Subjects with a known or suspected hypersensitivity to iron were also excluded.

Study Design and Drug Administration

This was a single-center, double-blind, randomized, placebo-controlled, single-ascending-dose study to evaluate the pharmacokinetics, serum iron profile, and tolerability of single intravenous doses of ferric pyrophosphate citrate iron in healthy subjects. Cohorts of 8 subjects each (6 randomized to drug and 2 randomized to placebo) were consecutively enrolled in the study and administered single doses of 2.5, 5.0, 7.5, or 10 mg of ferric pyrophosphate citrate iron or placebo via intravenous infusion over 4 hours or single doses of 15 or 20 mg of ferric pyrophosphate citrate iron or placebo via intravenous infusion over 12 hours. The 4-hour infusion time was chosen to mimic the usual time on dialysis, and the 12-hour infusion time was chosen to approximate the duration of infusion of total parenteral nutrition solutions. The maximal dose of ferric pyrophosphate citrate iron that can be administered by intravenous infusion without exceeding the total iron-binding capacity (TIBC) of serum was also determined in this study.

Ferric pyrophosphate citrate was supplied by Rockwell Medical, Inc (Wixom, Michigan) as a liquid concentrate formulation of 27.2 mg of ferric pyrophosphate citrate iron per vial (5.44 mg iron/mL). An appropriate volume of the stock solution for the required dose of iron was diluted in 500 or 1000 mL of 5% dextrose in water (D5W). The appropriate dose of ferric pyrophosphate citrate or placebo (D5W at a volume that corresponded to the volume of the ferric pyrophosphate citrate iron dose) was infused into a forearm by infusion pump at a rate of 62.5 mL/hour. Test materials were administered after a 12-hour fast, beginning at 8 AM.

Subjects were confined to the clinic from the evening before until the morning after administration of the test material and were given meatless meals during this period. A follow-up safety visit was conducted 1 week after discharge from the clinic. Safety data (including a serum iron profile and C-reactive protein [included to evaluate the potential for oxidative stress]) for a completed cohort, through the 1-week follow-up safety visit, were reviewed before the dose of drug was escalated to the next higher dose in the dose-escalation scheme.

Study Assessments

Blood samples for pharmacokinetic assessments of serum total iron (sFe_{tot}), transferrin-bound iron (TBI), and TIBC were obtained at –12 and –6 hours before the start of the 4- or 12-hour intravenous infusion (baseline measurements) and then immediately before (0 hour) and at 0.5, 1, 2, 3, 4, 4.5, 5, 6, 7.5, 8, 9, 10, 12, 12.5, 14, 16, 20, 24, 36, and 48 hours after the start of the 4-hour intravenous infusion or immediately before and at 0.5, 1, 2, 4, 4, 6, 9, 12, 12.5, 14, 16, 18, 20, 24, 30, 36, and 48 hours after the start of the 12-hour intravenous infusion. Additional blood samples were obtained immediately before and immediately after the end of the 4- or 12-hour infusion for measurement of concentrations of serum hepcidin-25, serum sTfR, and serum biomarkers of oxidative stress (isofuran, F2-isoprostanes, and malondialdehyde [MDA]) and inflammation (interleukin-6 [IL-6]).

Safety was monitored through a review of the nature, frequency, and severity of adverse events, safety laboratory tests, vital signs, ECGs, and physical examinations.

Bioanalytical Methods

Serum total iron and TBI were measured using an assay that was specifically validated with ferric pyrophosphate citrate iron to measure concentrations of total iron and TBI. Briefly, total serum iron was determined after liberation of bound iron and reduction with dithionite via reaction with Ferene. TBI was measured after dilution of the sample and addition of 4 mM ni-

triloacetic acid (NTA) to capture nonspecifically bound iron, among which is iron bound to albumin and citrate.[11] The diluted serum was passed through a polyimine solid-phase extraction (SPE) column to remove the NTA-iron complexes.[12] The iron content of the eluate from the SPE column was assayed for iron via the Ferene reaction after reduction with dithionite. Total protein content pre- and postcolumn was used to correct for concentration effects.[12] The assay performance was linear across a range of 20 to 3500 μg/dL. TBI accuracy and precision were determined across serum samples that were fortified with diferric transferrin and added to the matrix. Assay performance was accurate to within ±15% of the characterized target, and the coefficient of variation of all replicates was ≤15%.

Concentrations of serum sTfR were measured using quantitative immunoturbidimetry (ARUP Laboratories, Salt Lake City, Utah). Serum hepcidin-25 measurements were performed by a combination of weak cation exchange chromatography and time-of-flight mass spectrometry (WCX-TOF MS).[13] An internal standard (synthetic heavy hepcidin-25 stable isotope +40; custom made by Peptide International Inc, Louisville, Kentucky) was used for quantification.[14] The lower limit of detection of this method was 0.5 nM (reference range of serum hepcidin-25 in Dutch population, <0.5-14.7 nM for men, <0.5-12.3 nM for premenopausal women, www.hepcidinanalysis.com). The reference levels for the WCX-TOF MS method were derived from an enzyme-linked immunosorbent assay (ELISA) method[15] based on the regression line between the ELISA and WCX-TOF MS results that were obtained for the same samples from patients without hepcidin isoforms.[13]

Levels of free F2-isoprostanes in serum were measured by gas chromatography and mass spectroscopy.[16] Serum concentrations of IL-6 were determined by enzyme-linked immunosorbent assay (Quantikine Human IL-6 ELISA Kit, R & D Systems, Inc, Minneapolis, Minnesota).

Serum TIBC and serum ferritin concentrations were measured using standard automated clinical chemistry methods.

Pharmacokinetic and Safety Analyses

Concentrations of sFe_{tot} and TBI and pharmacokinetic parameters for sFe_{tot} were summarized using baseline-corrected values (mean of the values obtained at –12, –6, and 0 hours) to account for variability among subjects in serum iron concentrations before administration of the test material. Standard noncompartmental pharmacokinetic analyses in Phoenix WinNonlin (version 6.3, Pharsight Corp, Mountain View, California) were used to calculate the pharmacokinetic parameters of sFe_{tot}. Non-transferrin-bound
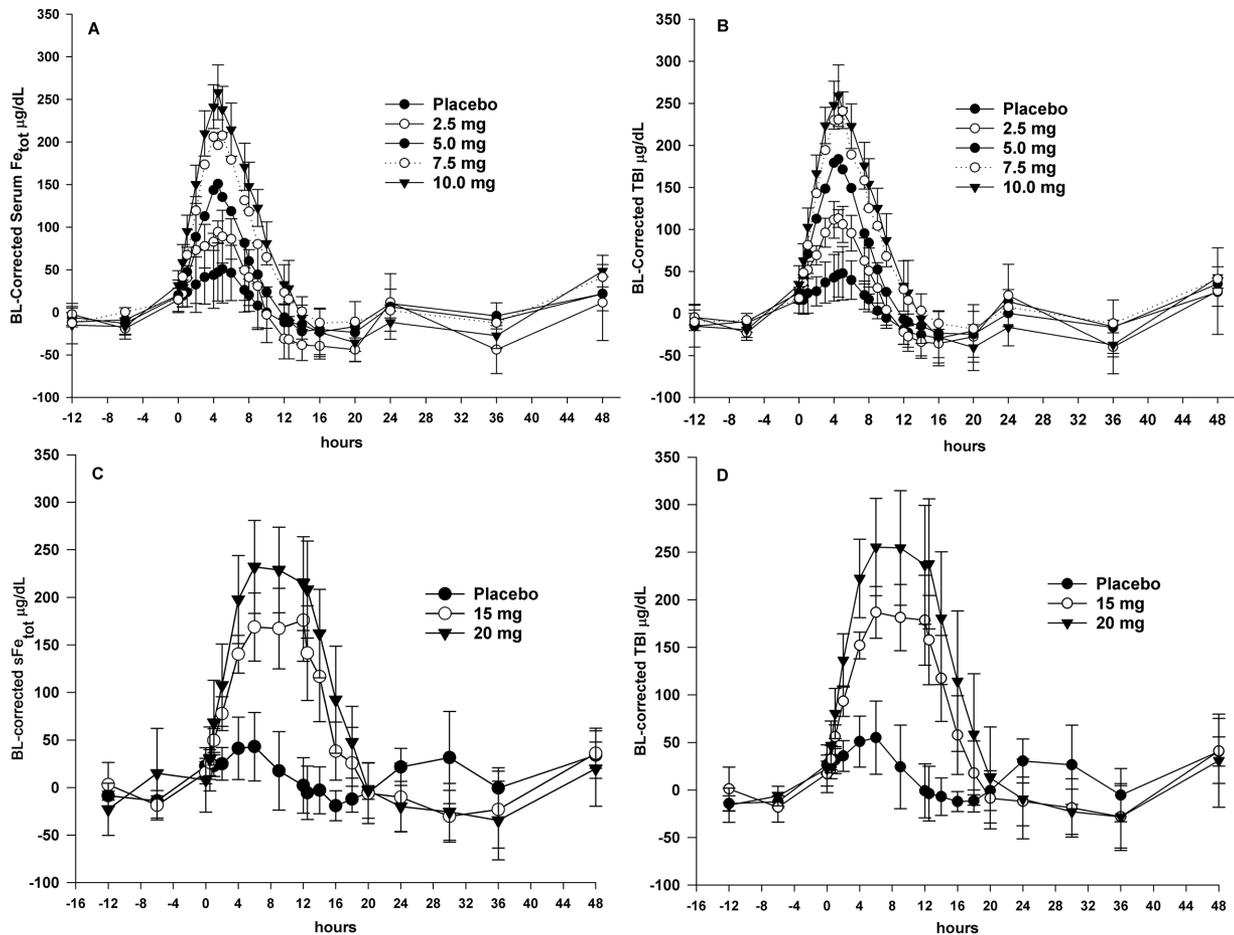
Figure 1. Concentration-time plots for serum total iron (sFe$_{tot}$) and transferrin-bound iron (TBI). (A and B) Mean baseline (BL)-corrected sFe$_{tot}$ and TBI concentration-time plots for 4-hour intravenous infusions of ferric pyrophosphate citrate iron (time 0-4 hours). (C and D) Mean BL-corrected sFe$_{tot}$ and TBI concentration-time plots for 12-hour intravenous infusions of ferric pyrophosphate citrate iron (time 0-12 hours). SD error bars are for placebo and highest dose only; error bars are similar for all doses.

iron (NTBI) was calculated as the difference between sFe$_{tot}$ and TBI. Transferrin saturation (TSAT) was calculated as TBI divided by TIBC times 100.

Pharmacokinetic parameters and continuous safety parameters were summarized with descriptive statistics. Categorical safety parameters were summarized with counts and percentages.

Results

Demographics
A total of 48 subjects (25 male and 23 female) were enrolled in the trial and randomized to receive single intravenous doses of ferric pyrophosphate citrate iron (n = 36) or placebo (n = 12). The subjects were primarily white (81%) and ranged in age from 19 to 55 years (mean 30 years). No relevant differences in demographic characteristics, including the baseline serum iron parameters (sFe$_{tot}$, TIBC, TSAT, or ferritin), were observed among the individual cohorts or between

the combined ferric pyrophosphate citrate iron and combined placebo treatment groups overall.

Pharmacokinetics
The placebo treatment groups demonstrated marked diurnal variation in sFe$_{tot}$ and TBI (Figure 1A-D), with peak concentrations observed between 4 and 5 hours after the start of infusion. Infusion of ascending doses of ferric pyrophosphate citrate iron over 4 or 12 hours showed a progressive dose-proportional increase in baseline-corrected sFe$_{tot}$ and TBI concentrations, with maximum serum concentrations (C$_{max}$) observed at the end of the 4- or 12-hour infusion (Figure 1A-D). Changes in absolute TSAT followed the changes in sFe$_{tot}$ and TBI concentrations (Figure 2).

Iron was rapidly cleared after intravenous administration, with a mean apparent terminal-phase half-life (t$_{1/2app}$) of 1.2 hours for the 4-hour and 2.0 hours for the 12-hour intravenous infusion (Table 1). The values for sFe$_{tot}$ were dose proportional for C$_{max}$ and area
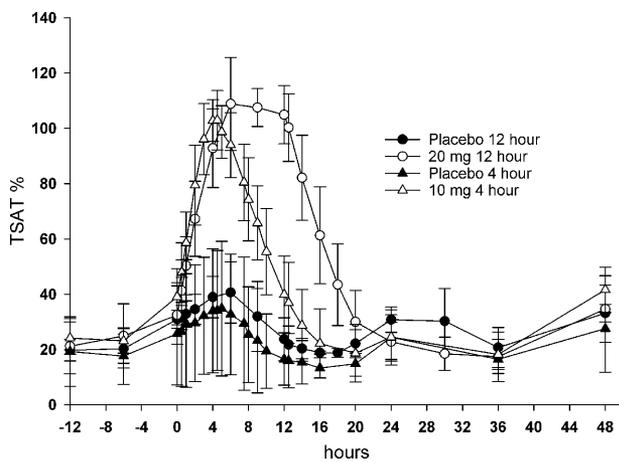
Figure 2. Absolute transferrin saturation (TSAT) over time for placebo, 10 mg of ferric pyrophosphate citrate iron administered as a 4-hour intravenous infusion, and 20 mg of ferric pyrophosphate citrate iron administered as a 12-hour intravenous infusion.

under the serum concentration-time curve from 0 to the time of the last quantifiable concentration (AUC_{0-t}) (Figure 3A,B).

The concentration-time course of sFe_{tot}, TBI, and NTBI after administration of the 10-mg dose as a 4-hour intravenous infusion is shown in Figure 4. Concentrations of NTBI did not increase with increasing dose (data not shown). An in vitro study of ferric pyrophosphate citrate iron added to plasma-like medium showed that ferric pyrophosphate citrate iron can generate labile plasma iron (LPI) in the presence of ascorbate (Supplemental Figure S1). This ability was markedly decreased in an ex vivo study when ferric pyrophosphate citrate iron was added to human plasma. Significant amounts of LPI (Supplemental Figure S2) and NTBI (Supplemental Figure S3) were observed only when the iron concentration exceeded 100% TSAT.

Hepcidin-25, sTfR, and Oxidative Stress and Inflammatory Biomarkers

Serum hepcidin-25 concentrations were within published reference ranges for men and premenopausal women for the assay used at baseline and at the end of each of the 4- and 12-hour infusions. No change from baseline in serum hepcidin-25 concentration was observed at the end of 4-hour infusions of 2.5, 5, 7.5, or 10 mg of ferric pyrophosphate citrate iron (Figure 5). A 3.2- to 7.4-fold increase in serum hepcidin-25 concentration was observed at the end of the 12-hour infusions of 15 and 20 mg of ferric pyrophosphate citrate iron, but values remained within normal ranges for men and premenopausal women (Figure 5). Serum hepcidin-25 concentrations returned to baseline for all doses by 24 hours after the start of infusion.

The change from baseline in serum sTfR concentration, expressed as the fold change in concentration at the end of infusion vs baseline, declined as the TSAT at the end of infusion increased (Figure 6). A similar trend was observed for the sTfR vs log ferritin index (data not shown). The largest declines in serum sTfR concentration were observed after 12-hour infusion of the 15- and 20-mg doses. Values for serum sTfR had returned to preinfusion values for each of the doses by 24 hours after the start of infusion.

Values for the biomarkers of oxidative stress (serum isofuran, F2-isoprostanes, and MDA) and inflammation (serum IL-6) were unchanged from baseline at the end of infusion (Figure 7). A statistically significant difference was observed between ferric pyrophosphate citrate and placebo in the mean change from baseline in serum isofuran concentration at the end of the 12-hour infusion ($P \leq .05$, Wilcoxon test); however, serum F2-isoprostanes did not show a similar change.

Table 1. Baseline-Corrected Pharmacokinetic Parameters for sFe_{tot} in Healthy Volunteers After Intravenous Administration of Ferric Pyrophosphate Citrate Iron

Pharmacokinetic Parameter[a]	FPC Iron Dose (mg) 4-Hour Intravenous Infusion					FPC Iron Dose (mg) 12-Hour Intravenous Infusion		
	0	2.5	5.0	7.5	10.0	0	15.0	20.0
C_{max}, μg/dL	62.6 (32.4)	113 (44.5)	151 (33.9)	228 (19.7)	261 (30.3)	44.3 (34.8)	177 (38.2)	251 (51.7)
λ_z, 1/h	–	0.5 (0.1)	0.7 (0.3)	0.7 (0.4)	0.9 (0.7)	–	0.5 (0.3)	0.3 (0.1)
$t_{½app}$, hours	–	1.3 (0.2)	1.2 (0.5)	1.3 (0.7)	1.0 (0.5)	–	1.9 (1.1)	2.2 (0.6)
CL, dL/h	–	4.1 (1.2)	5.1 (1.0)	4.6 (0.5)	5.6 (0.9)	–	6.7 (1.6)	6.6 (1.5)
t_{max}, hours[b]	–	4.9	4.3	4.8	4.3	–	8.5	7.8
AUC_{0-t}, μg · hr/dL	–	675 (270)	1010 (190)	1650 (172)	1840 (263)	–	2340 (565)	3150 (657)

AUC_{0-t}, area under the serum concentration-time curve from 0 to the time of the last quantifiable concentration; CL, total drug clearance; C_{max}, maximum serum concentration; FPC, ferric pyrophosphate citrate; λ_z, terminal rate constant; sFe_{tot}, serum total iron; $t_{½app}$, apparent terminal-phase half-life; t_{max}, time to maximum serum concentration.

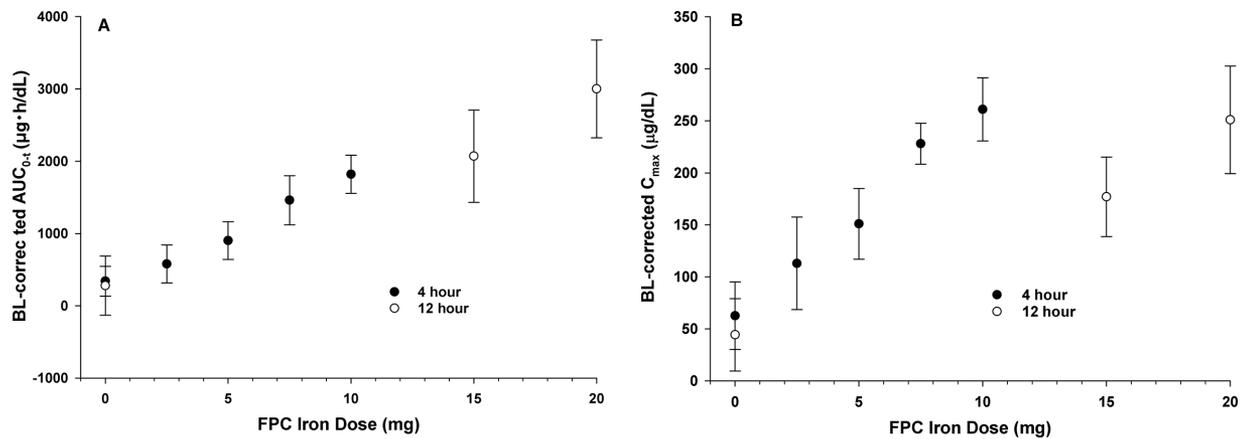[a]Values are expressed as mean (SD) unless otherwise indicated.
[b]Median value.

Figure 3. Mean (SD) baseline-corrected exposure parameters for serum total iron (sFe$_{tot}$) by ferric pyrophosphate citrate (FPC) iron dose. (A) Area under the concentration-time curve from 0 to the time of the last quantifiable concentration (AUC$_{0-t}$). (B) Maximum serum concentration (C$_{max}$).
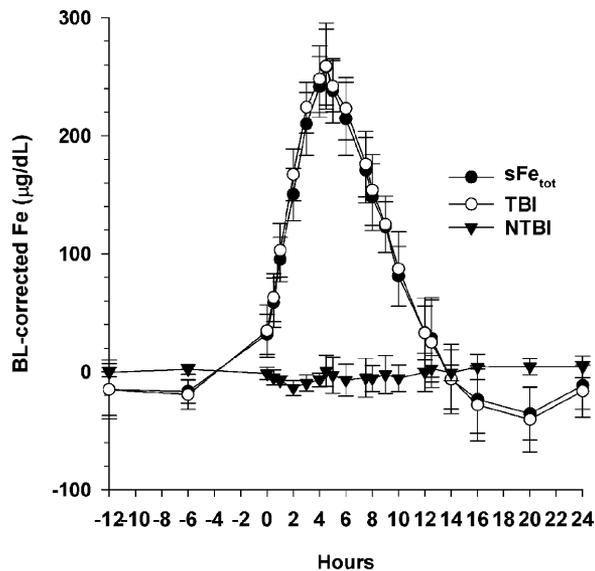

Figure 4. Mean (SD) baseline (BL)-corrected serum total iron (sFe$_{tot}$), transferrin-bound iron (TBI), and calculated non–transferrin-bound iron (NTBI) concentrations after administration of 10 mg of ferric pyrophosphate citrate iron as a 4-hour intravenous infusion.
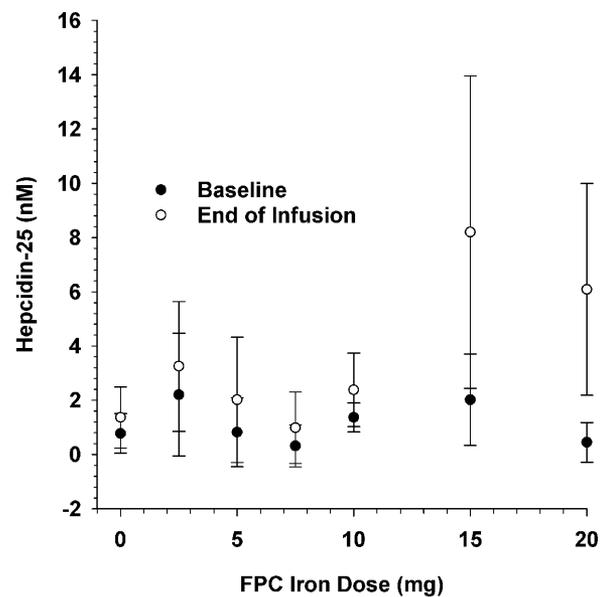
Figure 5. Mean (SD) serum hepcidin-25 concentrations at baseline and at the end of infusion as a function of ferric pyrophosphate citrate (FPC) iron dose.

Safety

Intravenous doses of ferric pyrophosphate citrate were well tolerated. At least 1 adverse event was reported in 9 of the 36 subjects (25.0%) who received ferric pyrophosphate citrate and in 3 of the 12 subjects (25.0%) who received placebo. Headache (7 of 36, 19.4%) and dizziness (2 of 36, 5.6%) were the most commonly reported adverse events in the ferric pyrophosphate citrate–treated subjects. No relationship was observed between the incidence of these events and the dose of ferric pyrophosphate citrate iron or the duration of the intravenous infusion. None of the reported adverse events were severe or considered to be related to ferric pyrophosphate citrate. No clinically relevant abnormalities were observed in laboratory test results, vital signs, ECGs, or physical examinations.

Discussion

This study was conducted in healthy male and female volunteers to examine the pharmacokinetics of intravenously administered ferric pyrophosphate citrate iron. Ferric pyrophosphate citrate iron differs from the currently available forms of intravenous in several key features. Intravenous iron preparations are large macromolecular carbohydrate iron complexes designed to utilize the RBC salvage pathway to metabolize and release iron to transferrin.[17] Intravenous injection of nanoparticulate iron can also lead to the appearance
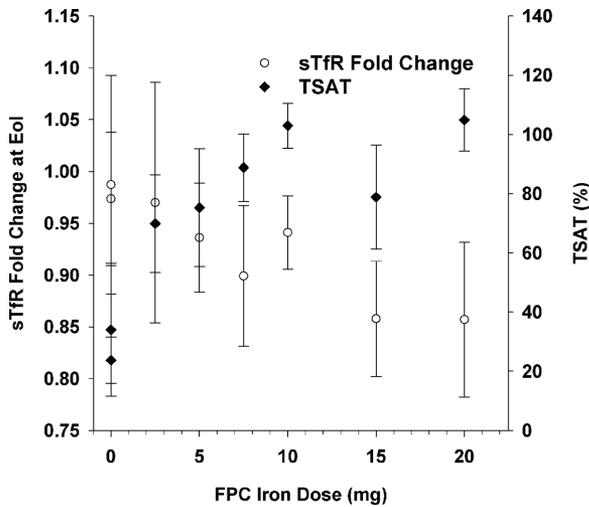
Figure 6. Mean (SD) fold change from baseline in serum soluble transferrin receptor (sTfR) and transferrin saturation (TSAT) at end of infusion as a function of ferric pyrophosphate citrate (FPC) iron dose.

of NTBI,[18] which may be taken up in an unregulated manner by cells of the endocrine, cardiac, and hepatic systems.[19] A portion of circulating NTBI is readily available to participate in redox cycling and is referred to as catalytic iron or LPI, which contributes to redox activity and the production of free radicals and oxidative stress.[20,21] The pharmacokinetics of the currently approved intravenous iron products also demonstrate a heterogeneity in clearance from the circulation, with a $t_{\frac{1}{2}app}$ of 1.4 hours for sodium ferric gluconate, 5.3 hours for iron sucrose, 7.4 to 9.4 hours for ferric carboxymaltose, and 14.7 hours for ferumoxytol.[22]

Ferric pyrophosphate citrate iron is administered in small quantities at each hemodialysis session to replace the ongoing iron losses in patients with CKD-5HD.[23] The pharmacokinetics of ferric pyrophosphate citrate iron are distinctly different from intravenous iron preparations in that all administered iron is bound to transferrin, with a rapid clearance similar to that of intravenously administered diferric transferrin ($t_{\frac{1}{2}app}$ 80-120 minutes).[24] All of the administered ferric pyrophosphate citrate iron is donated to transferrin as indicated by the high concordance of total serum iron to TBI. Negligible NTBI is found at TSAT up to 100% after administration of ferric pyrophosphate citrate iron. The 4-hour infusion of ferric pyrophosphate citrate resulted in hepcidin-25 concentrations that were not different from those with placebo. The 12-hour infusion resulted in a small increase in hepcidin-25 concentration because the higher quantity of iron that was administered induced hepcidin.[25] The time course of serum hepcidin in response to oral iron peaks between 8 and 12 hours, so measurement of hepcidin at 4 hours may have missed a small increment in hepcidin, whereas the 12-hour infusion captured the iron-induced increase in hepcidin.[25]

The results of this study of intravenously administered ferric pyrophosphate citrate iron demonstrate dose-proportional pharmacokinetics up to a TSAT of 100%. Importantly, the results show that all of the delivered iron was complexed with transferrin and rapidly cleared from the circulation, with a median $t_{\frac{1}{2}app}$ of 1.2 to 2.0 hours.

No induction of biomarkers of oxidative stress or inflammation was observed after administration of intravenous doses of ferric pyrophosphate citrate iron over the range of 5 to 20 mg, with the exception of a slight increase in serum isofuran concentrations, which was considered to be random because no concurrent change was observed in serum F2-isoprostane or MDA concentrations. In contrast, intravenous administration of iron sucrose and iron sucrose plus vitamin C has been shown to increase levels of serum F2-isoprostanes and inflammatory cytokines in healthy volunteers and in hemodialysis patients.[26] A meta-analysis of 34 studies that examined the impact of intravenous iron in
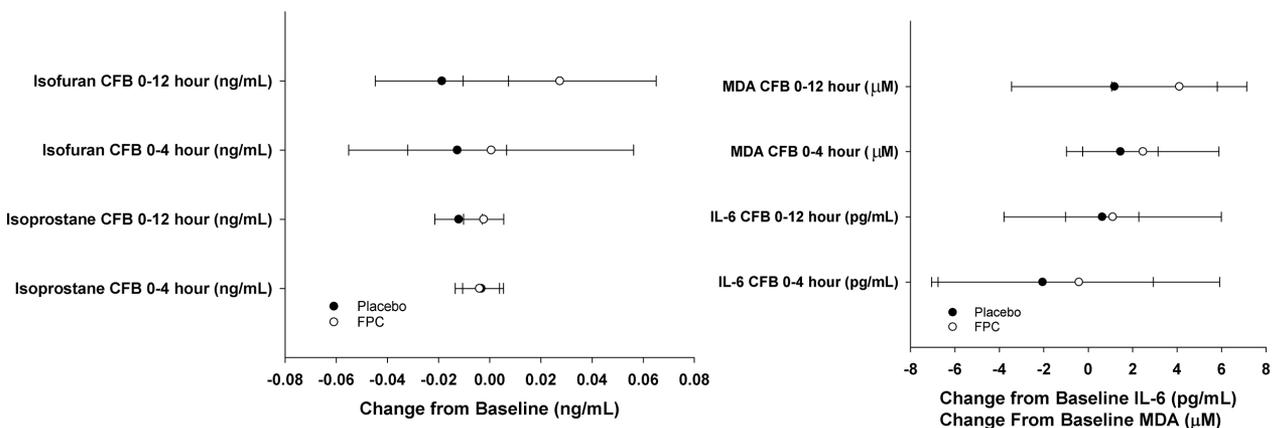

Figure 7. Change from baseline (CFB) in serum biomarkers of oxidative stress (isofuran, F2-isoprostanes, and malondialdehyde [MDA]) and inflammation (interleukin-6 [IL-6]) at end of infusion for ferric pyrophosphate citrate (FPC) iron and placebo.

hemodialysis patients concluded that intravenous iron supplementation improved hemoglobin concentration but was associated with effects on oxidative stress biomarkers of uncertain clinical significance.[27] The results of this study of intravenously administered ferric pyrophosphate citrate iron in healthy volunteers confirm the results of previous clinical studies of ferric pyrophosphate citrate in patients with CKD-5HD, which have shown no changes in biomarkers of oxidative stress or inflammation over a 9-month period.[28]

Intravenous doses of 2.5, 5.0, 7.5, and 10 mg of ferric pyrophosphate citrate iron were well tolerated when administered over 4 hours and intravenous doses of 15 and 20 mg of ferric pyrophosphate citrate iron were well tolerated when administered over 12 hours, with no significant safety findings observed at any dose.

In conclusion, the results of this study show dose-proportional pharmacokinetics after intravenous administration of ferric pyrophosphate citrate iron up to a TSAT of 100%, with all iron donated directly to transferrin. Apparent serum clearance of iron was rapid, consistent with the clearance of diferric transferrin. A maximum dose of 10 mg of ferric pyrophosphate citrate iron can be administered intravenously over 4 hours (typical duration of hemodialysis), and up to 20 mg of ferric pyrophosphate citrate iron can be administered intravenously over 12 hours. The pharmacokinetic and safety profiles indicate that ferric pyrophosphate citrate iron may be a suitable for maintenance iron therapy in patients with CKD-5HD. The safety of 15 to 20 mg of intravenous ferric pyrophosphate citrate iron over 12 hours in this normal volunteer study suggests that intravenous infusion of ferric pyrophosphate citrate iron also merits investigation for the treatment of functional iron deficiency in nondialysis patients with anemia of inflammation secondary to high serum hepcidin concentrations and in patients who receive total parenteral nutrition.

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