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Pharmacokinetic Study of Ferumoxytol: A New Iron Replacement Therapy in Normal Subjects and Hemodialysis Patients

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Key Words
Intravenous iron · Ferumoxytol · Iron pharmacokinetics · Renal anemia · Chronic kidney disease

Abstract
Background: Currently available intravenous iron preparations are not ideal, either because of safety concerns or dose limitations. We investigated the safety and pharmacokinetics of ferumoxytol, a new iron replacement therapy, in normal subjects and hemodialysis patients. ***Methods:*** In a randomized, double-blind, ascending-dose study in normal volunteers (n = 41), 6 subjects received placebo, and 8 subjects each received ferumoxytol, at 1, 2 or 4 mg iron/kg, injected at 60 mg iron/min. The remaining subjects received 4 mg iron/kg at injection rates of 90 (n = 3), 180 (n = 3) or 1,800 mg iron/min (n = 5). In the second, open-label, ascending-dose study, 20 hemodialysis patients received 125 or 250 mg of iron over 5 min. ***Results:*** In normal subjects, the blood half-life of ferumoxytol increased with increasing dose from 9.3 to 14.5 h ($p < 0.05$) but not with increasing rate of injection. The drug half-life in hemodialysis patients was similar to normal subjects. Ferumoxytol was not removed with hemodialysis. Serum iron ($p < 0.001$), transferrin saturation ($p < 0.001$) and ferritin increased in both populations. No serious adverse events were attributable to ferumoxytol. ***Conclusion:*** Ferumoxytol was well tolerated in this study. Its pharmacokinetic properties and simplicity of administration suggest that it will be an attractive form of iron replacement therapy.

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Introduction

Normocytic, normochromic anemia is a common and treatable complication of chronic kidney disease (CKD) and end-stage renal disease (ESRD). According to the USRDS 2001 annual data report, there is a significant increase in the relative risk of cardiac, infectious, and all-cause mortality in ESRD patients with hematocrits <33% [1] and an even greater risk in patients with hematocrits <30%. Although multiple factors contribute to the anemia of CKD, the primary cause is insufficient production of endogenous erythropoietin (EPO). Effective treatment

This work was performed at the University of Virginia Health System and at Jersey Shore Medical Center.

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of this anemia is associated with improved survival, decreased morbidity, and increased quality of life. Higher hematocrits have also been associated with marked improvements in various physiological parameters including oxygen utilization, muscle strength and function, cardiac function, possible regression of left ventricular hypertrophy, improvement in exercise tolerance and exercise-induced ST segment depression, cognitive and sexual function [2–7].

EPO use in hemodialysis patients has led to the successful treatment of anemia in most ESRD patients [8]. However, several factors can decrease the effectiveness of EPO including aluminum toxicity, hyperparathyroidism, infection, inflammatory conditions, malignancy, and, most importantly, iron deficiency [9]. Absolute iron deficiency in hemodialysis patients occurs for a variety of reasons, including blood retention in the dialysis membranes and connecting tubing system [9], occult gastrointestinal blood loss [10, 11], blood loss during surgery, frequent blood sampling [12], and increased erythropoiesis from the use of EPO [12]. Functional iron deficiency also occurs where adequate tissue iron stores are present but unavailable for erythropoiesis.

The estimated prevalence of iron deficiency in hemodialysis patients during EPO therapy is around 43–90% [9, 13, 14]. According to the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (KDOQI) anemia guidelines [2], patients should have sufficient iron to achieve and maintain a hemoglobin of 11–12 g/dl and a hematocrit of 33–36%. To accomplish this, the guidelines suggest administering sufficient iron to a maintain transferrin saturation (TSAT) of $\geq$20% and a serum ferritin $\geq$100 ng/ml [2]. Many studies have shown that oral iron is generally ineffective in maintaining adequate stores in most dialysis patients [3, 15, 16], as well as in patients not yet on dialysis [3, 16, 17]. Consequently, intravenous iron is commonly used to achieve and maintain adequate iron levels. Although intravenous iron replacement can be given over 10 min (125 mg iron gluconate) or 5 min (100 mg iron sucrose), it is generally given over 15–60 min, which requires significant expense for supplies such as tubing and infusion supplies, costly nursing time, multiple administrations, and may be inconvenient for the patient.

Until 1999, iron dextran was the only intravenous iron preparation available in the USA. Since then, iron gluconate and iron sucrose have become available for intravenous use. Although serious and life-threatening reactions occur most frequently with iron dextran [18], they do occur rarely with iron gluconate and iron sucrose [19, 20]. In addition, non-life-threatening reactions such as hypotension, back pain, vomiting, vertigo, and pruritus also occur with the gluconate and sucrose formulations and may be related to the rate of administration [20, 21]. These reactions, although not life-threatening, will sometimes preclude further dosing and therefore iron repletion [19, 22–24]. Finally, there is concern regarding the potential deleterious effects of parenteral iron in increasing oxidative stress and infection, and accelerating cardiovascular disease.

We examined the safety and pharmacokinetics of a new compound for iron replacement therapy, ferumoxytol, administered as an intravenous bolus, first in 41 healthy volunteers in a placebo-controlled, dose and injection rate escalation study, and then in 20 chronic hemodialysis patients receiving EPO therapy.

Materials and Methods

Ferumoxytol

The study drug, ferumoxytol (Advanced Magnetics, Inc., Cambridge, Mass., USA), is an ultrasmall superparamagnetic iron oxide (magnetite) nanoparticle coated with a semisynthetic carbohydrate designed to minimize immunological sensitivity. The drug has an average colloidal particle size of 30 nm by light scattering and a molecular weight of 750 kDa. Ferumoxytol is a sterile, isotonic, neutral pH liquid formulated to contain 30 mg/ml of elemental iron and 44 mg/ml of mannitol. Because of its magnetic properties, ferumoxytol can also be used as a magnetic resonance contrast agent.

Study Designs

Both trials were approved by Institutional Review Boards and conducted in accordance with the guidelines proposed in the Declaration of Helsinki, under an Investigational New Drug Exemption. All patients gave written informed consent to be in the study.

Normal Subjects. This phase I safety and pharmacokinetic study was a randomized, double-blind, placebo-controlled, ascending-dose study in adult male and female volunteers (n = 41). Subjects were 18–60 years old, not anemic, and in good general health. Eight subjects each received ferumoxytol at doses of 1, 2 and 4 mg iron/kg at injection rate of 60 mg iron/min (2 ml/min). Six subjects received saline as a placebo. The remaining 11 subjects received ferumoxytol at 4 mg iron/kg at an injection rate of 90 (n = 3), 180 (n = 3) or 1,800 mg iron/min (n = 5).

For pharmacokinetic analysis, serial blood samples were taken pre-dose, 5, 10, 15, 30 min, and 1, 4, 8, 12, 24, 48, 72 and 168 h post-dosing. For safety assessment, blood and urine samples were taken at screening, 48 and 24 h pre-dosing, at 8, 24, 48 and 72 h, and 7 days post-dosing. Evaluations included a complete blood count, biochemistry panel, iron metabolism panel (serum iron, percent TSAT, transferrin, and ferritin) and clotting function tests. Resting 12-lead electrocardiograms were obtained at screening, and 48 h pre-dosing, at 15 min, 1, 4, 8, and 24 h, and 7 days post-dos-

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ing. Vital signs were obtained at the same time points and additionally at 1, 5, 10, 30, 45 min, and 2, 4, 48 and 72 h.

Hemodialysis Patients. The study in hemodialysis patients was an open-label, dose escalation study to assess the safety and pharmacokinetics of two doses of ferumoxytol in non-anemic chronic hemodialysis patients (n = 20) receiving EPO therapy for anemia. Subjects were at least 18 years old, currently undergoing outpatient hemodialysis three times a week and receiving EPO therapy; hemoglobin ≥11 g/dl and/or hematocrit ≥33% was required. Patients had not received oral or parenteral iron therapy for at least 2 weeks prior to entry; nor did they receive it for the duration of the study.

Two doses of ferumoxytol, containing 125 and 250 mg of elemental iron, were evaluated, given as an intravenous injection over 5 min, with the safety of the first dose established before proceeding to the higher dose. The first 10 patients were given a single dose of 4.2 ml of ferumoxytol (125 mg iron, 25 mg iron/min) and the second group of 10 patients was given a single dose of 8.4 ml of ferumoxytol (250 mg iron, 50 mg iron/min). Ferumoxytol was administered within 30 min of starting dialysis in all patients. No test dose was given.

Laboratory tests including complete blood count, electrolytes, comprehensive chemistry, hepatic function, iron metabolism panel and clotting function panel were drawn 1 week pre-dose, and at 48 h, 2 weeks, and 4 weeks following dosing. A panel consisting of complement levels (CH_{50} and C3) and a complete blood count with differential was drawn immediately pre-dose and at 60 and 180 min post-dose to assess complement activation.

Blood clearance samples were drawn immediately pre-dose and post-dose at 5, 10, 15, 30, 60, 120, 180 min, 48 h, and 96 h. Patients were evaluated for evidence of adverse reactions during and after the drug administration and at 48 and 96 h following drug administration.

Drug Concentration Quantification

Because ferumoxytol has strong magnetic properties (T1 relaxivity of 38 mmol s^{-1} and T2 relaxivity of 83 mmol s^{-1}) the intact, unmetabolized drug can be quantified by magnetic resonance spectrometer measurements [25], independent of serum iron, which has very low magnetic properties. The T1 spin-spin magnetic resonance relaxation time of the serum samples, standards, and controls were measured at 39.5°C using a Brucker PC-120 nuclear magnetic resonance spectrometer with an applied field of 0.47 T (20 MHz) using an inversion-recovery pulse sequence. The limit of detection of the assay was 3 μg/ml of ferumoxytol iron.

Safety Evaluation

Vital signs (blood pressure, heart rate, respiration rate and temperature) were evaluated at multiple time points before and after the drug administration in both studies. In addition, for the hemodialysis patients, the change in blood pressure recorded for each patient on the day of ferumoxytol injection was compared to the intradialytic blood pressure measurements recorded for that patient during the dialysis session 1 week prior to drug administration. Hypotension was considered an adverse event if the decrease in blood pressure was clinically significant based on the opinion of the investigator, regardless of the degree or absolute value.

Adverse events were identified by direct questioning and observation during drug administration, the post-administration observation period, and at later time points up to a week for the normal subjects and a month for the hemodialysis patients. A serious adverse event was defined as one which constitutes a definite hazard and/or results in a handicap to the patient, including but not limited to: death; a life-threatening adverse drug experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability/incapacity; chest pain, dyspnea or other evidence of anaphylaxis.

Statistical Analysis

Data are presented as mean ± SD. Two-way analysis of variance (ANOVA) with between-groups repeated measures was used to evaluate differences in laboratory measures and pharmacokinetic parameters between groups. The pharmacokinetic parameters were calculated assuming a first order process in a single compartment model, with a first order elimination rate constant (K_{el}), area under the curve (AUC) calculated by trapezoidal rule (t_{0h}–t_{48h}), maximum concentration (C_{max}) estimated as the instantaneous concentration at t = 0 and clearance calculated as volume of distribution (V_d) × K_{el}. Parameters were calculated using PK Solutions 2.0 (Summit Research Services, Pharmacokinetics and Metabolism Software, Montrose, Colo., USA).

Other Analyses

Although these were not efficacy trials, and neither volunteers nor hemodialysis patients were anemic, changes in hematologic parameters including serum iron, serum ferritin, TSAT, hemoglobin, hematocrit, and reticulocyte count were evaluated for evidence of iron utilization.

Results

Demographics

Normal Subjects. The study population was comprised of comparable numbers of men and women, and was predominantly black (63%), with an average age of 33.5 ± 7.7 years (table 1). Seven of these patients had ferritin levels <12 ng/ml; none had hemoglobin values <10.8 g/dl. The four treatment groups did not differ significantly with respect to gender, race, age, height, and weight.

Hemodialysis Patients. The study population included 20 patients (age 34–77 years; 10 women, 10 men, 70% black, see table 1) currently undergoing hemodialysis three times weekly at an outpatient dialysis unit. The first 10 patients recruited were assigned to the low-dose group (125 mg iron). After this dose was found to be well tolerated in this patient population, 10 additional patients were recruited to the high-dose group (250 mg iron).

Pharmacokinetics

Normal Subjects. The pharmacokinetic summary data including V_d, K_{el}, AUC, C_{max}, half-life, and clearance for the dose escalation arm of the trial are shown in table 2. The AUC and C_{max} increased significantly with dose, as

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Table 1. Subject characteristics

	Normal subjects	Hemodialysis patients
Number	41	20
Age	33.5 ± 7.7 (20–58)	60.7 ± 11.8 (34–77)
Gender, m/f	22/19	10/10
Race, B/W/H/O	26/8/7/0	14/5/0/1
Weight, kg	79.6 ± 15.1 (46.5–115.0)	84.2 ± 14.5 (55–107)
Height, cm	171.2 ± 9.8 (153.0–189.0)	168.4 ± 7.8 (157–183)
Hemoglobin, g/dl	13.0 ± 1.2 (10.8–16.0)	12.4 ± 1.0 (10.7–12.9)
Transferrin saturation, %	21.4 ± 7.6 (7.4–40.2)	29.6 ± 9.7 (14–47)
Serum iron, μg/ml	69.0 ± 20.7 (20–107)	58.8 ± 19.8 (32–99)
Ferritin, ng/ml	41.0 ± 32.5 (4–109)	259 ± 154 (86–677)

Table 2. Pharmacokinetic parameters at increasing dose, constant injection rate[a]

Parameter	Dose group		
	1 mg Fe/kg	2 mg Fe/kg	4 mg Fe/kg
Rate, ml/min	2	2	2
Rate, mg iron/min	60	60	60
Number	8	8	8
Mean dose, mg	85 ± 17	152 ± 30	321 ± 71
K_{el}, h^{-1}[b]	0.076 ± 0.010	0.069 ± 0.010	0.049 ± 0.007
Half-life, h[b]	9.3 ± 1.1	10.2 ± 1.5	14.5 ± 2.4
C_{max}, μg iron/ml[b]	26.3 ± 7.0	62.0 ± 11.6	126.0 ± 32.6
AUC, μg iron·h/ml[b]	396 ± 122	997 ± 320	2,771 ± 624
V_d, l	3.1 ± 0.8	2.4 ± 0.7	2.4 ± 0.6[d]
V_d, ml/kg	36.3 ± 10.0	31.1 ± 7.4	31.6 ± 8.5
Cl, ml/h[b]	235.8 ± 91.8	162.9 ± 52.4	115.7 ± 15.1
Cl, ml/(h·kg)[c]	2.82 ± 1.21	2.17 ± 0.63	1.51 ± 0.33

[a] Values are mean ± SD. K_{el} = First order rate constant; AUC = area under the curve; C_{max} = maximum plasma concentration of intact drug; half-life = elimination half-life; Cl = clearance; V_d = volume of distribution.
[b] Significant by dose, $p < 0.001$.
[c] Significant by dose, $p < 0.02$.
[d] Significant by gender, $p < 0.01$ (see text).

did the half-life, while clearance decreased ($p < 0.001$). The elimination half-life increased from 9.3 to 14.5 h from 1 to 4 mg of iron/kg. The high-dose group showed a statistically significant difference in V_d by gender, also observed in all groups but not at statistically significant levels. This difference is attributable to a lower body weight in the females, since total blood volume is proportional to body weight. The V_d per kilogram was not significantly different.

The pharmacokinetic results from the injection rate escalation are shown in table 3. There were no significant differences in the pharmacokinetic parameters with increasing administration rates. Including all subjects who received the dose of 4 mg iron/kg, a mean dose of 316 mg of iron in this study, the mean half-life is 14.7 h. The highest individual dose administered in this study was 420 mg of iron.

The concentration of ferumoxytol with time is shown in figure 1. The concentrations are dose-dependent ($p < 0.001$), and 90% of the highest dose is cleared from the blood by 48 h, approximately 3 half-lives.

Hemodialysis Patients. The pharmacokinetic summary data including V_d, K_{el}, AUC, C_{max}, half-life, and clearance are presented in table 4. The plasma pharmacokinetic parameters were similar to those observed in normal subjects. The half-life was different by dose ($p < 0.01$) as

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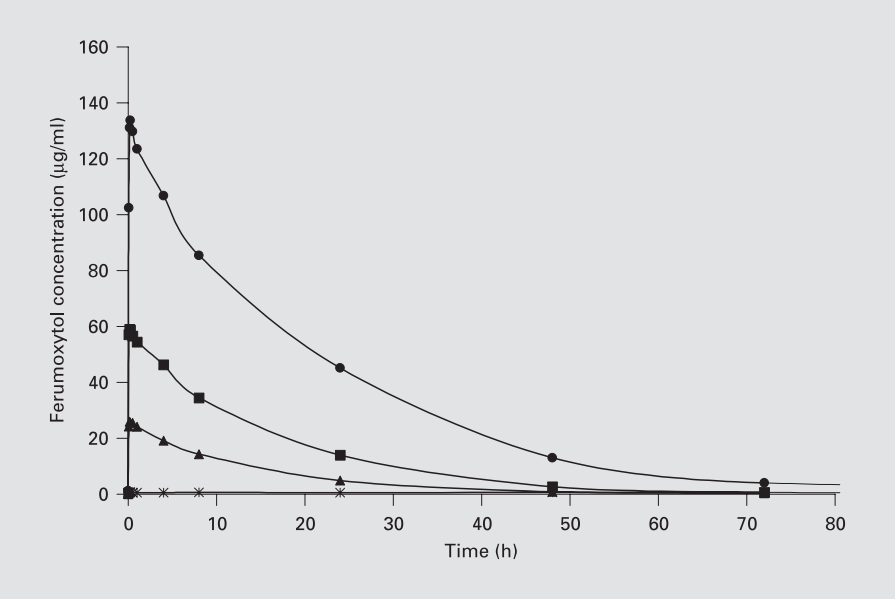

Fig. 1. Serum concentration of ferumoxytol with time in normal subjects by dose. ✳ = Placebo; ▲ = 1 mg/kg; ■ = 2 mg/kg; ● = 4 mg/kg. Concentration of ferumoxytol was dose-dependent ($p < 0.001$). The values are for intact drug and do not include serum iron.

Table 3. Pharmacokinetic parameters at increasing injection rate, constant dose[a]

Parameter	Administration rate group				
Dose, mg iron/kg	4[b]	4	4	4	4
Rate, ml/min	2	3	6	60	–
Rate, mg iron/min	60	90	180	1,800	–
Number	8	3	3	3	17
Mean dose, mg Fe	321 ± 71	323 ± 69	337 ± 45	273 ± 81	316 ± 66
K_{el}, h^{-1}	0.049 ± 0.007	0.049 ± 0.008	0.051 ± 0.005	0.043 ± 0.006	0.048 ± 0.007
Half-life, h	14.5 ± 2.4	14.5 ± 2.3	13.6 ± 1.4	16.2 ± 2.5	14.7 ± 2.2
C_{max}, µg iron/ml	126.0 ± 32.6	124.7 ± 31.1	141.4 ± 50.0	134.5 ± 30.3	130.0 ± 32.5
AUC, µg iron·h/ml	2,771 ± 624	2,857 ± 336	2,914 ± 984	3,343 ± 963	2,912 ± 683
V_d, l	2.4 ± 0.6	2.4 ± 0.9	2.4 ± 0.5	2.0 ± 0.4	2.3 ± 0.6
V_d, ml/kg	31.6 ± 8.5	29.6 ± 6.3	29.0 ± 9.3	29.1 ± 5.7	30.4 ± 7.3
Cl, ml/h	115.7 ± 15.1	116.1 ± 40.0	121.2 ± 27.1	83.2 ± 9.7	111.0 ± 24.1
Cl, ml/(h·kg)	1.51 ± 0.33	1.41 ± 0.18	1.47 ± 0.43	1.28 ± 0.43	1.44 ± 0.33

[a] Values are mean ± SD. K_{el} = First order rate constant; AUC = area under the curve; C_{max} = maximum plasma concentration of intact drug; half-life = elimination half-life; Cl = clearance; V_d = volume of distribution.
[b] Data in this group repeated from table 2, column 3, for comparison.

were C_{max}, AUC, and clearance ($p < 0.001$). The half-life was 10.7 h in the low-dose group and 16.2 h in the high-dose group, similar to that observed in normal subjects.

The concentration of ferumoxytol remained stable during the dialysis procedure, indicating that ferumoxytol is not removed with hemodialysis (fig. 2).

Laboratory Values

Normal Subjects. As expected, serum iron and TSAT increased in a dose-dependent manner, peaking at 1-day post-dose, whereas serum ferritin peaked at day 3; all returned toward baseline at 7 days. The changes in all were statistically significant ($p < 0.001$). The serum iron, TSAT, and serum ferritin are shown in figure 3.

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