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Sodium ferric gluconate complex in hemodialysis patients: Adverse reactions compared to placebo and iron dextran

Beckie Michael, Daniel W. Coyne, Steven Fishbane, Vaughn Folkert, Robert Lynn, Allen R. Nissenson, Rajiv Agarwal, Joseph W. Eschbach, Stephen Z. Fadem, J. Richard Trout, Jur Strobos, and David G. Warnock, for the Ferrlecit® Publication Committee[1]

Thomas Jefferson University, Philadelphia, Pennsylvania; Washington University School of Medicine, St. Louis, Missouri; Winthrop University Hospital, Mineola, and Montefiore Medical Center and Bronx Dialysis Center, New York City, New York; UCLA School of Medicine, Los Angeles, California; Indiana University, Indianapolis, Indiana; Northwest Kidney Center, Seattle, Washington; Houston Kidney Center, Houston, Texas; Rutgers University, New Brunswick, New Jersey; Washington, D.C.; and University of Alabama at Birmingham, Birmingham, Alabama, USA

Sodium ferric gluconate complex in hemodialysis patients: Adverse reactions compared to placebo and iron dextran.

Background. Parenteral iron is often required by hemodialysis patients to maintain adequate iron stores. Until recently, the only available form of intravenous iron was iron dextran, which is associated with significant adverse reactions, including anaphylaxis and death. Sodium ferric gluconate complex (SFGC) was recently approved for use in the U.S. under FDA's priority drug review. This Phase IV study was designed to evaluate the safety of a single dose of intravenous SFGC as compared to placebo and a historical iron dextran control.

Methods. This multicenter, crossover, randomized, double blind, placebo-controlled prospective comparative study was performed in hemodialysis patients requiring at least 125 mg of elemental iron. The historical control was obtained from a meta-analysis of four publications examining outcomes in patients exposed to iron dextran. SFGC naïve patients were administered SFGC without a test dose, undiluted, at a rate of 125 mg over 10 minutes, and compared to placebo comprising bacteriostatic saline.

Results. A total of 2534 patients were enrolled. The incidence of drug intolerance (an adverse event precluding re-exposure) was significantly less [0.44%, confidence interval (CI) 0.21 to 0.71%] after SFGC as compared to the iron dextran control (2.47%, CI 1.87 to 3.07%, $P < 0.0001$), but higher than after placebo (0.1%, $P = 0.02$). There was no difference found between SFGC and placebo in serious adverse events. A single life-threatening event occurred after SFGC (0.04%, CI 0.00 to 0.22%), which was significantly less than following iron dextran (0.61%, CI 0.36 to 0.86%), $P = 0.0001$.

Conclusion. SFGC is well tolerated when given by intravenous push without a test dose. SFGC has a significantly lower incidence of drug intolerance and life-threatening events as compared to previous studies using iron dextran. The routine use of iron dextran in hemodialysis patients should be discontinued.

[1] Other members of the Ferrlecit® Publication Committee, all of whom contributed equally to the preparation of this manuscript include: N. Franklin Adkinson (*Johns Hopkins University, Baltimore, MD*); Daniel Batlle (*Northwestern University Medical School, Chicago, IL*); Jose Cangiano (*San Juan Bautista School of Medicine, San Juan, Puerto Rico*); Jorge Diego (*University of Miami, Miami, FL*); Pam Myirski (*Baltimore, MD*); Chamberlain Obialo (*Morehouse School of Medicine, Atlanta, GA*); Chika Oguagha (*Nephrology Foundation of Brooklyn, New York City, NY*); S. Noor Rahman (*University of Texas at Houston, Houston, TX*); Steven Rosenblatt (*San Antonio Kidney Diseases Center, San Antonio, TX*); Andrea J. Shaer (*Medical University of South Carolina, Charleston, SC*); and Marcia R. Silver (*MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH*). Additional participants are listed in the **Appendix**.

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The increase in hemoglobin resulting from the use of erythropoietin in hemodialysis patients can be restricted by iron deficiency [1]. Blood loss from the extracorporeal hemodialysis circuit, vascular access complications, low-grade gastrointestinal bleeding and periodic phlebotomy has been estimated to be 2 to 4 liters per patient per year [2]. The concomitant iron loss, approximately 1500 mg annually, generally exceeds dietary iron absorption [3], resulting in a nearly universal need for supplemental iron therapy. In the majority of hemodialysis patients the use of oral iron is problematic, due to difficulties in patient compliance [4], and intestinal transport of iron that may be inadequate to meet epoetin-driven synthetic demands [5].

Parenteral iron has played an increasingly important role in anemia management in hemodialysis. Improvements in hemoglobin levels in dialysis patients over the

past five years appear to be due in part to the more widespread use of parenteral iron [6]. The use of parenteral iron in hemodialysis patients is endorsed by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) [7]. K/DOQI guidelines for anemia management recommend the use of parenteral iron not only for absolute iron deficiency, but also for functional iron deficiency, where iron stores are present but cannot be mobilized rapidly enough to maintain maximal epoetin-driven erythrogenesis [7]. In the United States (U.S.), the increased use of parenteral iron has come at a price: the only preparation available until February 1999, iron dextran, can cause anaphylaxis and death. Life-threatening anaphylactoid reactions occur in approximately 0.7% of iron dextran treated hemodialysis patients [8], and serious drug intolerance that precludes further administration occurs in at least 2.5% of patients [8–10]. Since 1976 at least 30 deaths in the U.S. have been attributed to iron dextran use [11]. While a test dose of iron dextran is recommended prior to initiating full therapy, deaths have occurred subsequent to the test dose itself, before a course of iron dextran treatment [12, 13]. The antigen that induces anaphylaxis in iron dextran is thought to be the dextran molecule rather than the iron moiety. Dextran is composed of glucose polymers of varying size and its early use, as a volume expander, was associated with anaphylaxis [14]. Alternative intravenous iron preparations, which do not contain dextran, have been used for many years outside of the U.S. Sodium ferric gluconate in sucrose injection (sodium ferric gluconate complex: SFGC) is widely used in Europe. There have been no reported fatalities due to SFGC, with a European usage estimated to be similar, in terms of total doses administered, as that of iron dextran in the U.S. [11]. While hypersensitivity reactions have been anecdotally associated with SFGC, serious reactions have rarely been reported.

Sodium ferric gluconate complex was approved in the U.S. in 1999 under the Food and Drug Administration's (FDA's) priority review program, with a requirement for an extensive Phase IV safety analysis. The clinical data compiled before FDA approval included only 385 prospective patient experiences from two controlled studies and published reports [15–19]. While these data were supplemented by many years of European clinical experience in which the incidence of spontaneous adverse events was not significant [16], international consensus guidelines recommend a minimum prospective drug exposure experience in 1500 patients before approval [20]. Priority review approval has often been based on small study populations and, thus, may lack comprehensive long-term efficacy and safety data. To address these concerns, FDA requires Phase IV post-approval studies to increase patient exposure experience, study the effects of concomitant medications, evaluate risks in special sub-populations, or gather longer term safety information [21, 22]. Twelve of the last 20 (60%) new agents approved by FDA under the priority review program were subject to such clinical Phase IV studies, in contrast to only one of the last 20 (5%) approved under standard review [21, 22]. Complex design and ethical issues are involved in Phase IV safety studies, including the use of placebo controls to evaluate clinically available and effective products [23–25]. FDA has not required placebo controls in most Phase IV safety studies. This could limit rigorous safety evaluation, especially in patients with concomitant illnesses and poly-pharmacy, which may predispose to adverse experiences. Placebo controls may be essential for assessment of drug safety in such patients.

This report describes a novel approach to Phase IV drug safety evaluation using placebo controls in a single-dose, crossover study designed to evaluate the safety of a single dose of intravenous SFGC as compared to placebo and a historical iron dextran control. This is the largest controlled prospective study ever carried out in the hemodialysis population.

METHODS

The study was a multicenter, crossover, randomized, double-blind, and prospective, comparative study of the safety of SFGC in hemodialysis patients. The response to SFGC was compared to two controls: placebo and a historical control identified from a meta-analysis of publications describing rates of events in patients exposed to iron dextran formulations. The iron dextran control group was not concurrent because of the drug's known high adverse event profile, and the paucity of iron dextran-naïve patients in the U.S. hemodialysis population. The final study design was approved by the FDA.

Study objectives

The study had two primary objectives: (*a*) to compare subjectively identified drug intolerance events and life-threatening adverse events after SFGC administration to the two controls (concurrent placebo and historical iron dextran); and (*b*) to assess the safety of SFGC when administered by intravenous push at a rate of 12.5 mg/min. Drug intolerance events were defined as any event that would preclude further study drug administration. Life-threatening adverse events were defined as any immediate reaction requiring institution of resuscitative measures other than those typically used during dialysis to treat common intra-dialytic complications. Secondary objectives were to determine the rate of all adverse events following the administration of SFGC; to compare the incidence of all adverse events following SFGC and those following placebo; to determine the incidence of all adverse events in SFGC-treated patients receiving

angiotensin-converting enzyme inhibitor (ACEI) therapy as compared to patients not receiving such therapy; and to evaluate cross-reactivity to iron dextran.

Patient selection

Patients were enrolled at 69 centers in the U.S. between August 1999 and October 2000. All centers obtained approval from their respective Institutional Review Boards; each patient provided written informed consent. Eligible patients were adult hemodialysis patients on chronic dialysis and supplemental epoetin therapy for more than 120 days. Inclusion in the study required hemoglobin <13.5 g/dL, serum ferritin <800 ng/mL and transferrin saturation <50%. Patients with known allergy to iron dextran were not excluded from the study. However, to avoid over-enrollment of atopic or multiple drug allergy patients, which could bias the study toward over-reaction, no center could enroll more than 10% of patients with an iron dextran allergic history. This limit was based on an estimate of a naïve population rate of any allergy to iron dextran of less than 8% based on the meta-analysis. Patients were excluded from the study if they had prior treatment with SFGC, had known sensitivity to benzyl alcohol or were undergoing acute or chronic therapy with antihistamines or corticosteroids. Patients who would require a first time exposure to a new type of dialyzer membrane during the study were excluded. Additional exclusion criteria included: the recent need for volume removal at an average rate of >1 L/h per 70 kg patient; a Kt/V <1.2 or URR <65%; serum albumin <3.0 g/dL; repeated missed treatments during the three months prior to the study; signs and symptoms of, or undergoing treatment for, an infectious disease; presence of an active malignancy; suspicion or presence of unstable angina; history of stroke or symptoms of cerebral vascular insufficiency within the previous six months; the inability to maintain normal oxygen saturation; any blood glucose >400 mg/dL or <50 mg/dL during the two weeks prior to the study; hospitalization within 30 days of the first hemodialysis session of the study; and any use of an investigational agent within seven days of the first study session.

Study design

Patients who satisfied the inclusion criteria and signed informed consent participated in the study that included four sequential hemodialysis sessions. The first session consisted of screening procedures, medical history, review of medications, allergy history and physical exam. Randomization sequences were computer generated centrally using a 1:1 ratio. At the second session, patients were randomized into one of two crossover treatment schedules: SFGC at HD session number 2 and placebo at HD session number 3; or placebo at HD session number 2 and SFGC at HD session number 3 (Fig. 1). At hemodialysis session number 4 the patient was assessed for inter-dialytic adverse reactions and the study was completed. A single dose of 125 mg of SFGC was administered undiluted by IV push over a period of 10 minutes. Placebo was composed of 10 mL of bacteriostatic saline (containing 9 mg/mL of benzyl alcohol) and was administered at the same rate as SFGC. Both placebo and SFGC were prepared by unblinded personnel; each syringe was covered so that the personnel administering the drug and reporting adverse events were blinded to the treatment. Drug or placebo was administered during the first 60 minutes of the dialysis procedure. Vital signs (blood pressure and pulse) were recorded at baseline, five minutes into the injection and at five and 20 minutes after completion of the infusion. Any adverse reaction that occurred during study drug infusion was recorded and classified as an instantaneous reaction, while one that occurred during the ensuing dialysis session was considered an immediate reaction. Before the initiation of dialysis at the subsequent session, patients were reassessed for any intervening adverse events, which were considered delayed reactions.

Historical iron dextran control

Rates of reactions to iron dextran were obtained from four published studies [8–11]. These studies had similar designs and totaled 3768 patient exposures to different iron dextran formulations (Imferon®, Fisons PLC, Pharmaceutical Division, Crewe, Cheshire, UK; InFeD®, Watson Pharmaceuticals Inc., Corona, CA, USA; Feridex®, Advanced Magnetics, Inc., Cambridge, MA, USA) in different patient populations (post blood loss, hemodialysis, oncology). The validity of the historical iron dextran control was confirmed by review of the actual events included as life-threatening events in these studies. Rates of drug intolerance and life-threatening events were calculated from these studies by three independent medical observers and the results validated by two independent biostatisticians. In Hamstra, Block and Schocket's study design, an event had to be documented in the medical record and require medical intervention for greater than one hour to be considered life-threatening (3/481; 0.62%) [9]. In Fishbane et al's study, an event had to be documented in the dialysis record and require hospitalization to be considered life-threatening (4/573; 0.70%) [8]. In the Feridex® control, an event had to be life-threatening, characterized as an anaphylactic reaction, require intervention and preclude re-exposure (11/2240; 0.49%), but suspected non-allergic events identified as acute pain with substantial hypotension requiring drug discontinuation were not included as life-threatening anaphylactic events [10]. In the Faich and Strobos survey of multiple hospital discharge databases, an event required contemporaneous administration of iron dextran and intrave-

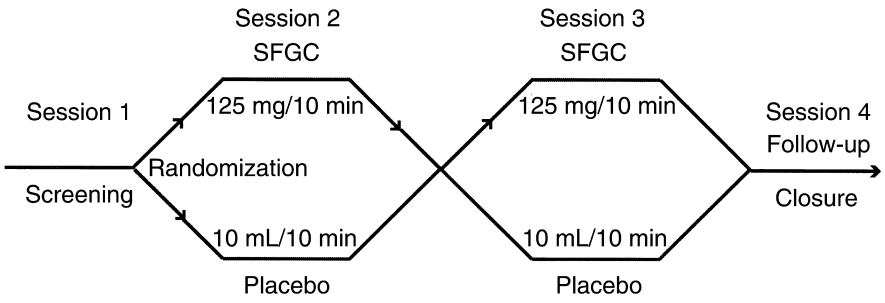

Fig. 1. Study design.

nous epinephrine in a hospitalized dialysis patient to be included (5/474; 1.1%) [11]. Thus, the historical iron dextran reaction rate was designed to underestimate the potential life-threatening reactions from iron dextran as compared to the prospective arm of the study, which required only the subjective determination by the investigator that the reaction was sufficiently severe to require any acute immediate medical intervention beyond that typically provided during dialysis.

Statistical methods

The study was powered to ascertain an 80% likelihood of identifying a 0.5% difference in life-threatening and drug intolerance event rates between SFGC and iron dextran. Confidence intervals (CIs) were constructed around both the prospective event rates and the rate from the historical control. SFGC was to be defined as superior to iron dextran only if there was no overlap between the 95% CIs of the prospective life-threatening and drug intolerance event rates and that of the historical iron dextran event rate, thus ensuring a minimum of four standard deviations between the means to establish superiority. Additional analyses included comparison of all adverse events between SFGC and concurrent placebo control using McNemar's test, which excludes patients who react to both arms. Evaluations of cross-reactivity in prior reactors to iron dextran and the effect of concomitant medications (ACEI) on various reaction rates were performed by logistic regression analysis. Statistical significance was declared if the P value using a two-sided Fisher's exact test was ≤ 0.05. A FDA-mandated blinded interim analysis was performed on the first 1106 patients, assuming that all observed adverse events were attributable to SFGC. Because the double blind had not been broken, and the design remained unchanged, the study continued and no statistical penalty for the interim analysis was assessed at the final analysis of the unblinded data.

RESULTS

A total of 2534 hemodialysis patients were enrolled in 69 dialysis centers. Their demographics and baseline characteristics are summarized in Table 1 by sequence assignment. Patient demographics demonstrated a high percentage of African American (58%) and Hispanic (18%) patients relative to the United States Renal Data System patient mix, but consistent with the demographics of the site locations. There was no difference in demographics among sequence groups or among patients who discontinued compared to those that completed the study.

Forty-four patients (44/2534; 1.7%) discontinued participation after receiving a single study drug infusion so that 2514 received SFGC and 2509 received placebo (one patient inadvertently received drug at both sessions), Table 2. Of these 44, seven (0.3%) patients discontinued participation for failure to meet continuing eligibility criteria for drug administration at the second consecutive dialysis session (for example, inadvertent self-administration of antihistamines, discovery of an elevated transferrin saturation or serum ferritin), seventeen (0.7%) patients withdrew consent during the study, and nine (0.4%) patients withdrew for various logistical reasons such as intra-study transplantation or failing to return for the second consecutive hemodialysis session. Of the 44 dropouts, only eleven patients (11/2534; 0.4%) withdrew following adverse events. Of these 11, nine events were deemed unrelated intercurrent events by the blinded investigator and/or required hospitalization and thus study discontinuation. Of these nine, five received SFGC only (chills, pneumonia, hypertension, clotted AV fistula, and fever) and four received placebo only [sepsis (2), abdominal pain, and cholelithiasis]. Two (2/2534; 0.08%) discontinuations for adverse events were deemed related to study drug administration: hypotension (received SFGC only); and, abdominal pain and diarrhea (received placebo only).

Twenty-two patients from a single site were excluded from analyses evaluating the study endpoints (life-threatening events, drug intolerance events, and relationship to iron dextran sensitivity and concomitant ACEI therapy). During data analysis, local errors in randomization records at that single site were discovered that could not be corrected. These patients were not excluded from other analyses (all adverse events and serious adverse events).

Table 1. Summary of patient demographics

Characteristics	SFGC-placebo $N = 1264$ N (%)	Placebo-SFGC $N = 1270$ N (%)	Total $N = 2534$ N (%)
Age *years*			
Mean ± SD	55.7 (15.1)	56.1 (15.0)	55.9 (15.0)
Range (min–max)	19–92	19–91	19–92
Gender			
Male	680 (54%)	718 (56%)	1398 (55%)
Female	584 (46%)	552 (44%)	1136 (45%)
Race			
Caucasian	276 (22%)	275 (22%)	551 (22%)
Black	728 (58%)	733 (58%)	1461 (58%)
Asian-Oriental	21 (2%)	23 (2%)	44 (2%)
Hispanic	224 (18%)	227 (18%)	451 (18%)
Native American	2 (0.2%)	1 (0.1%)	3 (0.1%)
Other	13 (1%)	11 (1%)	24 (1%)
Cause of renal failure			
Diabetes mellitus	431 (34%)	459 (36%)	890 (35%)
Hypertension	506 (40%)	512 (40%)	1018 (40%)
Glomerulonephritis	119 (9%)	116 (9%)	235 (9%)
Other	261 (21%)	218 (17%)	479 (19%)
Prior iron dextran exposure			
Yes	1157 (92%)	1181 (93%)	2338 (92%)
No	106 (8%)	89 (7%)	195 (8%)

Table 2. Summary of patient disposition

	By treatment sequence		
Disposition	SFGC-placebo	Placebo-SFGC	Total
Enrolled and included in safety analysis	1264	1270	2534
Included in outcome analysis	1254	1258	2512
	By treatment		
	SFGC	Placebo	Total
Discontinuations	24	20	44
Adverse events	6	5	11
Protocol violation	2	5	7
Consent withdrawn	11	6	17
Other	5	4	9
Completed study	1240	1250	2490

None of these patients experienced a study endpoint event after either placebo or SFGC.

After completion of the study, one patient was diagnosed with acute dermal symptoms from the genetic disorder porphyria cutanea tarda, which the investigator attributed to study iron therapy. This event, identified as a drug intolerance event, was manually re-assigned to SFGC despite the original assignment to placebo, the last drug received.

Drug intolerance

Among SFGC treated patients, 11 (0.4%) experienced a reaction deemed serious enough to preclude re-exposure to study drug. Among placebo treated patients, 2 (0.1%) experienced such drug intolerance events ($P = 0.02$; Table 3). Clinical characteristics of drug intolerance following SFGC were: two patients with pruritus and one patient each with anaphylactoid reaction, hypotension, chills, back pain, nausea, dyspnea/chest pain, facial flushing, rash and cutaneous symptoms of porphyria. The two intolerance reactions following placebo were hypotension and severe gastrointestinal complaints with nausea, itching and flushing.

Table 3. Protocol-defined adverse events: SFGC vs. placebo control

Event	SFGC $N = 2493$ N (%)	Placebo $N = 2487$ N (%)	P value (McNemar's)
Life-threatening	1 (0.04%)	0 (0%)	NA
Drug intolerance	11 (0.4%)	2 (0.1%)	0.02

There were significantly fewer drug intolerance events in patients receiving SFGC as compared to the iron dextran control (Table 4). Results of the three studies used

Table 4. Adverse events: SFGC vs. historical iron dextran control

Event	SFGC	Iron dextran	Confidence intervals	*P* value
	%, *N*, CI			
Life-threatening	0.04% 1/2493 0.00–0.22%	0.61% 23/3768 0.36–0.86%	No overlap	0.0001
Drug intolerance	0.44% 11/2493 0.21–0.71%	2.47% 64/2589 1.87–3.07%	No overlap	<0.0001

CI denotes 95% confidence interval.

for the historical iron dextran control demonstrated a combined drug intolerance rate of 2.47% ± 0.31% (95% CI 1.87 to 3.07%) [8–10], whereas drug intolerance events occurred in just 11/2493 (0.44%, 95% CI 0.21 to 0.71%, $P < 0.0001$) patients receiving SFGC, thereby meeting predefined criteria for superiority.

Life-threatening reactions

Only one event in the study was characterized as life threatening, and it occurred after completion of an SFGC infusion. This patient had several drug allergies including past anaphylactoid reactions to both forms of commercially available iron dextran as well as allergic reactions to both penicillin and cephalexin. He was not on an ACEI. Four minutes after the SFGC infusion was completed, the patient developed severe low back pain, nausea and became diaphoretic. He subsequently vomited a small amount of clear fluid and complained of shortness of breath. Wheezing was noted on chest exam. Intravenous diphenhydramine, intravenous hydrocortisone and subcutaneous epinephrine were administered between 10 and 15 minutes after drug infusion was completed and deemed necessary resuscitative interventions. All symptoms resolved 20 minutes after the infusion was completed. Hemodialysis was completed and the patient went home on schedule without any sequelae. Since only one patient experienced a life-threatening event during the study, it was not possible to compare the incidence of this event rate between SFGC and placebo (Table 3), although confidence intervals clearly overlap.

There were significantly fewer life-threatening events in patients receiving SFGC as compared to the historical iron dextran control (Table 4). Results of the four studies used for the historical iron dextran control demonstrated a rate of life-threatening reactions of 0.61% ± 0.13% (95% CI 0.36 to 0.86%) [8–11]. Life-threatening events occurred in only one of 2493 (0.04%, 95% CI 0.00 to 0.22%; $P = 0.0001$) of patients receiving SFGC, thereby meeting predefined criteria for superiority in safety.

All adverse events

The percentage of patients who experienced at least one adverse event during the study (related and unrelated) was 18.2% (460/2534). Although the incidence of all adverse events was similar between SFGC (309/2514; 12.3%) and placebo (246/2509; 9.8%), the difference was statistically significant by McNemar's test after exclusion of the 95 patients with reactions to both arms ($P = 0.0008$). The historical data for iron dextran could not be analyzed for this endpoint. Overall, 5.4% of patients experienced an adverse event that was considered by the investigator to be possibly related to study drug: 97 (3.9%) following SFGC and 62 (2.5%) following placebo ($P = 0.0006$).

With regard to serious adverse events, no difference in rate between events following SFGC (14, 0.6%) and placebo (12, 0.5%) could be identified ($P = 0.8450$). Similarly, no significant relationship in serious adverse events deemed related by the investigator was identified between SFGC (3, 0.1%) and placebo (1, 0.04%; $P = 0.63$). The three events possibly related to SFGC were hypotension, pruritus and the previously described life-threatening event. The single event possibly related to placebo was sepsis with rigors.

Adverse events by body system and type of event

The cardiovascular and digestive systems were the only two body systems for which adverse events occurred statistically more frequently among patients receiving SFGC as compared to placebo ($P \leq 0.05$). In the cardiovascular system category, 5.4% (136/2514) of SFGC-treated patients and 4.1% (103/2509) of placebo-treated patients had an adverse event recorded. Within the digestive system category, 64 (2.5%) of 2514 patients experienced an event following SFGC and 39/2509 (1.6%) experienced an event following placebo. Among all body systems, the COSTART preferred terms that occurred more frequently after SFGC as compared to placebo ($P < 0.05$) were back pain, hypertension, dyspepsia and nausea. Given anecdotal reports of gastrointestinal symptoms following SFGC, an analysis was conducted to identify whether any combination of nausea, vomiting, diarrhea, abdominal pain or hypotension occurred more commonly following SFGC than placebo. The most common combination of reported events for both SFGC and placebo was nausea and vomiting (0.6%; 15/2534). This was also the only combination for which a statistically significant difference was observed between patients receiving SFGC (12/2514, 0.5%) and those receiving placebo (4/2509, 0.2%; $P = 0.04$).

Hypotension; hypotension and flushing

There was no significant difference in post-administration hypotensive events following SFGC (97/2514; 3.8%) as compared to placebo (84/2509; 3.3%; $P = 0.25$). Of these, 36 patients had hypotension following both placebo and SFGC. Three episodes of combined hypotension and flushing occurred during the study: two following SFGC and one following placebo ($P = 0.25$).

Iron dextran cross-reactivity

A total of 2338 patients (92.3%) enrolled in the study had prior exposure to iron dextran. Sensitivity to iron dextran was present in 144 of these patients, of which 34 patients had a sensitivity classified as anaphylactoid. Among patients with previous sensitivity to iron dextran, the rate of serious adverse events to SFGC was 0.7% (1/144) compared to 0.6% (12/2173) in patients with no previous sensitivity (P = NS). As noted above, the only life-threatening reaction occurred in a patient with a history of multiple drug allergies including anaphylaxis to iron dextran. The rate of all adverse events to SFGC in patients with prior iron dextran sensitivity was 11.1% (16/144) versus 12.3% (268/2173) in patients without such sensitivity, and logistic regression failed to show an interaction between reaction to SFGC and prior iron dextran sensitivity ($P = 0.6957$). Logistic regression also failed to identify cross-reactivity between SFGC and iron dextran in either drug intolerance events or serious adverse events. Of note, 127 of 144 (88%) patients with iron dextran sensitivity reported no reaction of any kind following SFGC administration.

Interaction with concomitant ACEI therapy

Seven hundred and seven (707/2534; 28%) patients received concomitant ACEI therapy. Of these, 95 of 704 (13.5%) had an adverse event following SFGC and 63 of 697 (9.0%) following placebo administration. Among patients without concomitant ACEI therapy, the reaction rates were similar: 11.8% (214/1810) following SFGC and 10.1% (183/1812) following placebo. Logistic regression failed to show an interaction between concomitant ACEI therapy and events following SFGC as compared to placebo ($P = 0.1097$). Among patients with either suspected allergic events or drug intolerance, there were 15 reactions following SFGC and 6 reactions following placebo. Among the SFGC assigned reactions, 0.9% (6/698) occurred in patients on ACEI and 0.5% (9/1795) in patients not on ACEI. Among placebo-assigned reactions, 0% (0/691) occurred in patients on ACEI and 0.3% (6/1796) in patients not on ACEI. Logistic regression failed to show any relationship to incidence or severity of reaction in association with concomitant ACEI therapy.

DISCUSSION

The results of this study demonstrate the superior safety profile of SFGC. In comparison to iron dextran, the drug that has been the mainstay of intravenous iron support for hemodialysis patients in the U.S., SFGC was found to be considerably safer. The rate of life-threatening reactions with SFGC compared to iron dextran was 0.04% versus 0.61%, a reduction in risk of 93%. Furthermore, the only life-threatening reaction in this study completely resolved after 20 minutes, allowing the patient to complete his hemodialysis treatment without the need for hospitalization. This reaction would not have been classified as life threatening in two out of the four historical iron dextran controls. Although certainly severe in nature, this reaction to SFGC must be contrasted to reactions with iron dextran, which often require hospitalization and may lead to death. The drug intolerance rate to SFGC was also statistically lower than the iron dextran control group. Although more drug intolerance events were seen in SFGC treated patients as compared to placebo, no difference in serious adverse events could be found. The excess events following SFGC, as compared to placebo, were predominately gastrointestinal in nature. In contrast to an anecdotal report of the combination of flushing and hypotension following SFGC administration [26], our study found no difference in the incidence of hypotension or hypotension and flushing following SFGC as compared to placebo. Zanen et al also postulated that oversaturation of transferrin and free iron toxicity is responsible for adverse reactions to SFGC [26]. Transferrin saturation was not measured immediately after SFGC administration in their study. However, Seligman et al, using a more specific assay, studied this issue and found that oversaturation of transferrin did not occur after administration of 125 mg of SFGC (abstract; Seligman et al, *J Am Soc Nephrol* 11: 297A, 2000). As recognized by others [27], the description of transferrin oversaturation by Zanen et al [26] most likely resulted from the use of an invalid analytic method that did not differentiate between drug-bound iron and endogenous transferrin-bound iron (abstract; *ibid*).

Treatment of iron deficiency with intravenous iron is uniquely important in the hemodialysis setting. Epoetin therapy is administered to the vast majority of these patients as treatment for anemia, with a target hemoglobin of 11 g/dL to 12 g/dL [7]. Response to treatment is highly variable, with iron deficiency often blunting the effectiveness [17, 28]. Iron deficiency develops in most hemodialysis patients, caused by persistent blood retention in the dialysis lines and filter, diminished dietary iron absorption, and insufficient availability of circulatory iron during the intense erythropoietic stimulation of epoetin therapy [29]. A series of studies have demonstrated that oral iron treatment has limited efficacy compared to intravenous iron in this patient population [4, 17, 30–35]. Intravenous iron therapy has emerged as a standard of care, and the K/DOQI Anemia Clinical Practice Guidelines state that most epoetin-treated hemodialysis patients will require intravenous iron to maintain adequate iron stores [7]. In the last quarter of 1999, 61% of hemodialysis patients in the United States received treatment with intravenous iron [6]. The primary form of iron used for this purpose in the U.S. has been iron dextran, an effective medication, but one associated with

serious adverse events [8–11, 13]. Anaphylactoid reactions have been found to occur in 0.7% [8], and serious drug intolerance that precludes further therapy in 2.5% [8–10] of the patients treated with this drug. In a study by Fletes et al of patients experiencing an adverse event related to iron dextran, 26% required emergency room evaluation, 11% were hospitalized, and 0.6% (1/165) died [13]. Between 1976 and 1996, 31 deaths were reported in the United States as a result of exposure to intravenous iron dextran [11]. In contrast, during the same time period, no deaths were reported with SFGC use, despite similar rates of usage [11].

Sodium ferric gluconate complex has been used in Europe for nearly four decades, and clinical studies consistently demonstrated its excellent efficacy [16, 35]. However, because of the small study sizes and study designs not focused on the evaluation of safety, little could be concluded as to the safety of SFGC from the existing literature. SFGC was approved for use in the U.S. by the FDA under its priority review program in 1999. This report represents the first published large-scale, placebo-controlled Phase IV study devoted to safety evaluation of a priority-reviewed drug. Drug safety evaluation in patients with serious concomitant illness and polypharmacy, the context for priority-reviewed drugs, will often require placebo or similarly adequate controls. Anemic hemodialysis patients, for whom SFGC is indicated, frequently have hypotension, gastrointestinal symptoms, cramps, and other events that make a determination of true study drug-related events exceedingly difficult. In the post-approval setting, an ethical argument can be made that placebo controls are impermissible. Under the Declaration of Helsinki, placebo or no treatment controls are permissible only "in studies where no proven prophylactic, diagnostic and therapeutic method exists" [24]. We believe that this single-dose, crossover study design comports with these ethical constraints and should be more widely considered to study the incidence of acute reactions. In this study, each subject was provided active treatment and the exposure to a single dose of placebo was clinically inconsequential. The placebo as well as study drug contained preservative (benzyl alcohol) so that any reaction occurring after the study drug would be attributed only to SFGC. While one could be tempted to attribute the adverse reactions in the placebo phase to the benzyl alcohol in bacteriostatic saline, the minimal severity and low frequency of these placebo reactions would not warrant any direct evaluation of the reactions to bacteriostatic saline compared to normal saline.

The use of historical controls can be confounded by biases, including differences in patient populations and data collection. A historical iron dextran control was used because of its known high event profile as well as the paucity of iron dextran naïve patients in the current U.S. hemodialysis population. Although the iron dextran control group included patients that were repeatedly exposed to dextran, many reactions occurred on first exposure. As the studies used for the iron dextran control included retrospective chart reviews, the incidence of reactions to iron dextran was probably underestimated. In addition, the definition of life-threatening events in these studies was more stringent than that used in the current study. Although the use of a historical control is not ideal, the studies used in the meta-analysis reported similar rates of adverse events to iron dextran and provided an accurate reflection of the frequency of these events.

As our study demonstrates, reactions to SFGC seem to generally be mild and self-limited, and not of the catastrophic nature seen with iron dextran. An important exclusion criterion in this study was the concurrent use of antihistamines and glucocorticoids so as to maximize the detection of any adverse events in the study subjects. Such medications, especially antihistamines, are commonly given to hemodialysis patients and could conceivably minimize what were already mild reactions observed in a small proportion of the study subjects receiving SFGC.

An estimate of population impact of utilizing SFGC in place of iron dextran may be developed based on the approximately 200,000 hemodialysis patients in the United States, and annual treatment of 61% with intravenous iron [6]. The results of this study indicate a decrease in life-threatening reactions from 0.61% with iron dextran to 0.04% with SFGC, consistent with an annual reduction of 1140 such reactions, and a similar number of hospitalizations. In addition, concern over the risk of anaphylaxis with iron dextran may lead to physician reluctance to treat some patients who are iron deficient. As a result, such patients may experience inadequately treated anemia, with an increased risk for morbidity and mortality resulting from inability to achieve the target hematocrit [36–38].

Prior iron dextran exposure was present in the vast majority (92.3%) of study subjects, reflecting the common use of intravenous iron by the centers participating in this study. Sensitivity to iron dextran was found to occur in approximately 8% of patients exposed to iron dextran in the historical controls used for this study [8–10]. To prevent study enrichment with highly sensitized individuals, no site was permitted to enroll more than 10% of its subjects as iron-dextran sensitive patients. The actual study population included 144 (5.7%) individuals sensitive to iron dextran, 34 of whom had previously experienced dextran-related anaphylaxis. Because of the severity of these reactions, it is important to know whether such iron dextran sensitive patients also would react with SFGC. Although iron dextran sensitive patients were more likely to react to SFGC, they were also more likely to react to placebo. Logistic regression analysis failed to demonstrate cross-reactivity between SFGC and iron dextran in drug intolerance, all adverse

events and serious adverse events. These findings emphasize the value of placebo-controlled studies. The regression analysis takes into consideration that reactions following both placebo and SFGC were tenfold higher in patients with iron dextran sensitivity. The regression analysis suggests that this increased reactivity is not drug-specific. The one patient who experienced a life-threatening reaction following SFGC had multiple drug allergies, including a previous history of anaphylaxis to iron dextrans. Therefore, care should be used when administering SFGC to patients with a history of severe reactions with iron dextran or multiple drug allergies.

In a letter published in 1994, Rolla, Bucca and Brussino suggested that patients taking ACEI might be at increased risk for adverse reactions during intravenous iron gluconate therapy [39]. It also has been reported that black patients, who represented 58% of the study population, have a higher incidence of ACEI induced angioedema [40]. Seven hundred and seven patients (28%) in our study were receiving concomitant ACEI therapy. For all protocol-defined adverse events, there was no significant relationship between ACEI use and risk for reactions with SFGC. Since ACEI are commonly used for the treatment of hypertension and congestive heart failure, it is reassuring to note that SFGC may be safely used with this drug class.

The original package insert for SFGC recommended the use of a test dose prior to treatment [41]. This was in contrast to the European Best Practice Guidelines for The Management of Anemia, which does not make such a recommendation [42]. The use of a test dose is impractical because it requires nursing or physician monitoring and evaluation of the patient. For certain drugs with a high anaphylactic potential, a test dose helps to identify patients at risk in a controlled setting. The current study indicates that the risk for serious reaction with SFGC is very low. Therefore, there is no basis for the continued use of a test dose with this drug. The original package insert also recommended that SFGC be given by intravenous infusion over the course of one hour, as it was administered in the pivotal North American study [15]. More rapid intravenous administration would be more practical, and this study clearly demonstrates that SFGC administered intravenously at 12.5 mg/min is safe. Based on the FDA review of the blinded interim analysis of the results of the first 1106 patients, in which all of the adverse reactions were putatively attributed to SFGC, the warning of potentially severe hypersensitivity reactions was removed from the package insert for SFGC [43]. In addition, the revised package insert eliminated the need for a test dose, and intravenous infusion at a rate of 12.5 mg/min was included as a method of administration [43]. Intravenous administration at a rate more rapid than this should probably be avoided with all forms of intravenous iron.

Post-approval safety studies should be held to the same standards for rigorous design, review for subsequent publication in the medical literature, and product labeling as are applied to efficacy and pre-approval studies. Placebo controls can be used ethically in post-approval drug studies and should be encouraged. Although the FDA has declined to include placebo reaction rates in the labeling for SFGC, we suggest that such data are essential for physicians to identify and evaluate the true incidence of drug-related events, particularly in patients with chronic illnesses and polypharmacy, which predispose to adverse events.

In conclusion, this study demonstrates that SFGC is much safer than iron dextran. The administration of 125 mg of SFGC over 10 minutes without a test dose may be accomplished with few side effects. It would seem prudent to cease the routine use of iron dextran formulations in hemodialysis patients. The primary use of intravenous SFGC would result in a significant reduction in morbidity and perhaps mortality for hemodialysis patients with end-stage renal disease who require parenteral iron administration to achieve the anemia management goals described in the K/DOQI Anemia Clinical Practice Guidelines [7].

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Additional participating investigators

Michael Austerlitz (*Commerce, CA*); Habib Azad (*University of California Irvine Medical Center*); Raul Balagtas (*Tampa, FL*); Edwina Barnett (*Charles Drew University*); Mario Belledone (*Rockville, MD*); Jeffrey Berns (*University of Pennsyvania*); Anatole Besarab (*Henry Ford Health Systems*); Michelle Crage (*Woburn, MA*); Naomi Dahl (*Robert Wood Johnson Medical School*); Laura Dember (*Boston University Medical Center*); Devasmita Dev (*Veterans Administration North Texas Health Care*); Albert Dreisbach (*Tulane University School of Medicine*); Danny Fischer (*Cincinnati, OH*); Mary Gellens (*St. Louis University Medical College*); Michael Germain (*West Springfield, MA*); Elias Ghafary (*Gadsen, AL*); Charles Graeber (*Newington, CT*); Mandeep Grewal (*Chattanooga, TN*); Lee Hamm (*Tulane University School of Medicine*); Louisa Ho (*Evanston, IL*); Onyekachi Ifudu (*State University of New York*); Dennis Imperio (*Sarasota, FL*); Sam James (*University of Arizona Medical Center*); Mark Kaplan (*Nashville, TN*); Ellie Kelepouris (*Temple University School of Medicine*); Ken Kleinman (*University of California at Los Angeles*); Richard Lafayette (*Stanford University Medical Center*); David Leehey (*Loyola University Medical Center*); Susie Lew (*George Washington University Medical Center*); Jill Lindberg (*New Orleans, LA*); Thomas Marbury (*Orlando, FL*); Ronald Mars (*University of Florida*); Jeffrey Petersen (*Stanford University Medical Center*); Walter Piering (*Medical College of Wisconsin*); Russell Pikus (*Columbus, IN*); Rasib Raja (*Albert Einstein Medical Center*); Efrain Reisin (*Louisana State University Health Sciences Center*); Jeff Sands (*Emory University*); Steve Schwab (*Duke University Medical Center South*); Allan Schwartz (*Hahnemann University Hospital*); Warren Shapiro (*Brookdale, NY*); Anupkumar Shetty (*Henry Ford Health Systems*); Jerald Sigala (*Orange, CA*); Marcia Silver (*Cleveland, OH*); Richard Sires (*Ingelwood, CA*); David Spiegel (*University of Colorado Health Sciences Center*); Richard Swartz (*University of Michigan*); Kant Tucker (*Simi Valley, CA*); Nosratola Vaziri (*University of California Irvine Medical Center*); Sergio Vega (*West Palm Beach, FL*);

Kevin Vitting (*St. Joseph's Hospital and Medical Center*); Michael Walczyk (*Portland, OR*); Harry Ward (*Los Angeles, CA*); Robert Weiss (*Temple University*); Duane Wombolt (*Norfolk, VA*); and Elizabeth Wrone (*Palo Alto, CA*).

Reprint requests to Beckie Michael, D.O., Division of Nephrology, Thomas Jefferson University, 834 Walnut Street, Philadelphia, Pennsylvania 19107, USA.
E-mail: Beckie.Michael@mail.tju.edu

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