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Iron sucrose in hemodialysis patients: Safety of replacement and maintenance regimens

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Iron sucrose in hemodialysis patients: Safety of replacement and maintenance regimens.

Background. Parenteral iron replacement and maintenance are frequently required in hemodialysis patients. However, serious adverse events have been reported after single doses of some intravenous iron products. This multicenter phase IV clinical trial examined the safety of iron sucrose for the treatment of iron deficiency and for the maintenance of iron sufficiency in hemodialysis patients.

Methods. In this safety study, iron sucrose was given in two dosing regimens. Iron deficient patients were treated with intravenous iron sucrose, 100 mg, during 10 consecutive hemodialysis sessions (replacement regimen). Iron replete patients were given iron sucrose, 100 mg intravenous (iv) over 5 minutes, weekly for 10 weeks (maintenance regimen). At the end of each 10-dose cycle, iron status was reassessed, and dosing during the subsequent cycle was based on the adequacy of iron stores as per Dialysis Outcome Quality Initiative (K/DOQI) Guidelines. With each dosing regimen, adverse events, if any, were recorded and described.

Results. Six hundred and sixty-five hemodialysis patients, including 80 who had experienced previous intolerance to other parenteral iron preparations, received a total of 8583 doses of iron sucrose. One hundred eighty-eight patients received more than one iv iron cycle (replacement, maintenance, or both). There were no serious or life-threatening drug-related adverse events.

Conclusion. Iron sucrose is safe when given as treatment for iron deficiency or for maintenance of iron stores.

Hemodialysis patients require both iron replacement and iron maintenance therapy to optimize management of anemia. Because oral iron supplements are relatively ineffective in correcting iron deficiency and maintaining iron balance, clinical practice guidelines recommend administration of intravenous iron [3].

Key words: iron sucrose, hemodialysis, anemia, iron deficiency, safety.

Though intravenous iron products are effective in the treatment of the anemia of chronic kidney disease (CKD) [6, 17], serious adverse drug events have been reported with even single doses of some of these products [10, 16]. Iron sucrose has been used worldwide for more than 50 years [5]. Two multicenter studies have been performed in the United States to evaluate the safety and efficacy of iron sucrose injection in the treatment of dialysis-associated anemia [6, 19]. No serious drug-related adverse events or severe hypersensitivity reactions were seen in either study. However, both studies were relatively small, and both lacked information on maintenance iron regimens. To date, no large-scale, multicenter, multidose study has been reported to examine the safety of any intravenous iron compound given as repeated doses by multiple dosing regimens in a patient-management environment.

The current study was undertaken to examine the safety of iron sucrose under usual clinical situations. Because anemia management commonly includes both iron maintenance and iron replacement therapy, we sought to obtain information on iron safety using both iron dosing regimens. Accordingly, iron status was defined according to K/DOQI guidelines [3]. If the patient was iron deficient, the investigator used an iron replacement regimen. If the patient was iron replete, a maintenance regimen was used. Patients could receive multiple dosing cycles and either dosing regimen, depending upon their current iron status.

METHODS

Study design

This was a multicenter, open label, phase IV clinical trial in hemodialysis patients who required both

erythropoietin (EPO) and iron supplementation in accordance with the National Kidney Foundation K/DOQI Clinical Practice Guidelines [3]. Each 100 mg dose of iron sucrose (Venofer®, American Regent, Inc., Shirley, NY, USA) was administered intravenously by iv injection, undiluted, at 20 mg/min over 5 minutes.

Patient selection

Men or women over the age of 18, able to give informed consent, who were undergoing chronic hemodialysis 2 to 3 times weekly, and who met criteria [3] for parenteral iron and epoetin alfa were enrolled in the study. Patients previously intolerant to other parenteral iron products such as iron dextran and/or ferric gluconate were included. Pregnant or lactating women, patients with other severe concomitant diseases including active infection, patients with causes of anemia not related to either CKD or iron deficiency, or patients with a serum ferritin >800 ng/mL and or transferrin saturation (TSAT) >50% were excluded from enrollment in the study.

Drug regimens

Two dosage regimens of 10 doses of iron sucrose, 100 mg each dose, were given without a test dose. A replacement regimen (T) was given to patients who showed evidence of iron deficiency [3]. A maintenance regimen (M) was given to patients who were not iron deficient, but required maintenance of their iron needs. Patients received multiple dosing cycles and switched between replacement and maintenance cycles depending upon their iron status over the course of the study.

Replacement regimen

Patients were given an iron replacement regimen if baseline iron indices showed evidence of iron deficiency (TSAT <20%, serum ferritin <100 ng/mL, or both). These patients received 100 mg of iron sucrose at every hemodialysis session for 10 sessions to correct iron deficiency. At the end of a 10-dose cycle the patient's iron status was reevaluated no sooner than the dialysis day after the last iv iron dose [6]. Based on TSAT and serum ferritin values, patients received another replacement cycle (if still iron deficient), were started on a maintenance cycle (if TSAT was between 20% and 50% and serum ferritin was between 100 and 800 ng/mL, or received no further iron sucrose (TSAT >50% or ferritin >800 ng/mL).

Maintenance regimen

If TSAT was between 20% and 50% and the serum ferritin was between 100 and 800 ng/mL, inclusive, then a maintenance cycle was initiated and patients received iron sucrose, up to 100 mg, once weekly for 10 weeks. At the end of a 10-dose maintenance cycle, patients were reevaluated. At that time, iron could be stopped, patients could begin another maintenance cycle, or receive a replacement cycle to correct any iron deficiency, according to K/DOQI guidelines [3].

Termination/end of study criteria

Enrolled patients continued to receive replacement or treatment cycles according to the above protocol, based on the K/DOQI guidelines. Patients were free to withdraw from the study at any time. Patients experiencing a serious or unacceptable adverse event, whether related to the study drug or not, could be withdrawn at the discretion of the investigator. In addition, patients requiring renal transplantation or blood transfusion were withdrawn, as were those who were noncompliant with study procedures and protocols. The study was closed once sample size projections had been reached. We determined that a minimum of 460 patients would be adequate to detect a single anaphylactoid event with 90% power at an anaphylactoid reaction incidence of 0.005%.

Adverse events

At each dialysis session during the treatment period, and for 30 days after the last treatment dose was administered, we identified all serious adverse events and all drug-related adverse events in study patients by physical examination and direct inquiry of patients and patient records, using forms encoded for coding symbols for thesaurus of adverse events (COSTART). We defined serious adverse events, levels of severity of nonserious adverse events, and relationship of adverse event to study drug according to standard guidelines for clinical trials [1]. By these guidelines, a serious adverse event includes any experience that is fatal or life-threatening, results in or prolongs hospitalization, results in significant disability or incapacity, is unusual, or, in the opinion of the investigator, presents a significant hazard to the patient. Similarly, severity of adverse events is defined as follows: mild if causing no limitation of usual activity, moderate if causing some limitation, severe if causing inability to carry out usual activities. Relatedness of adverse events is defined as none, unlikely (temporal relationship between study drug and event is unclear and it is likely that the event can be explained by the subject's medical conditions or other therapies, including dialysis), possible (some temporal relationship between event and study drug administration, and event unlikely to be explained by the subject's medical condition or other therapies), or probable (temporal relationship is compelling and event cannot be explained by the subject's medical condition or other therapies). We defined iron sucrose intolerance as the inability to receive further iron sucrose therapy. It was the investigator's responsibility to identify, classify, and determine relatedness of adverse events and to designate study subjects as iron sucrose intolerant.

Table 1. Summary of baseline patient demographics, by initial dosage regimen

Characteristic	Initial dosage regimen	
	Replacement	Maintenance
Number of patients	337 (50.6%)	328 (49.3%)
Age $y \pm SD$	59.9 ± 14.9 (range 21–93)	58.5 ± 15.8 (range 21–92)
Sex *M:F*	194:143	207:121
Race (A:AA:C:H:O)[a]	10:133:153:37:4	5:159:133:29:2
Prior iron intolerance	58	22

[a] Asian: African American: Caucasian: Hispanic: Other.

Table 2. Summary of dosing cycles

Parameter	Dosing regimen		
	Replacement	Maintenance	Total
Number of doses	3910	4673	8583
Patients receiving 1 cycle	231	246	477 (71.7%)
Patients receiving 2 or more cycles	33	74	107 (16.0%)
Patients receiving both dosing regimens			81 (12.2%)

Statistical methods

All patients who received any amount of study drug were included in the safety analysis in an intent-to-treat fashion. Descriptive statistics were performed on safety parameters. Relative risks were calculated in order to determine the ratio of the risk of hospitalization or death per patient year due to infection in the iron sucrose group as compared to the United States Renal Data System (USRDS) historical control group [2, 4]. Chi-square tests were performed to calculate whether the proportions were statically significantly different between the two groups. A P value ≤ 0.05 was deemed statistically significant.

RESULTS

Patients

Six hundred and sixty-five patients were enrolled in the study. A summary of the baseline patient demographics is presented in Table 1. Eighty patients (12%) had a history of intolerance to an iron product administered prior to study enrollment: 63 to iron dextran alone; 5 to ferric gluconate alone; and 12 to both iron dextran and ferric gluconate. The mean duration of iron therapy was 101.4 days (median 79 days, range 9 to 439 days). Seventy-five percent of the patients remained on iron therapy for at least 138 days. Overall, data for analysis included evaluation of 239 patient years.

All 665 patients who received at least one dose of iron sucrose were included in the safety analysis. Of the 665 patients, 264 patients (39.7%) received replacement therapy for iron deficiency, 320 patients (48.1%) received maintenance regimens, while 81 patients (12.1%) received both replacement and maintenance iron regimens. Six hundred fifty-three patients were known to have been iron sucrose naïve, that is, not previously exposed to iron sucrose; one patient had received iron sucrose prior to study entry; and no specific information on iron sucrose exposure was available on the remaining 11 patients. Ninety-eight percent of the patients were receiving EPO at baseline.

Iron sucrose doses

A summary of iron sucrose dosing cycles is presented in Table 2. A total of 8583 doses of iron sucrose were administered; 3910 were given in replacement cycles and 4673 were administered in maintenance cycles. Forty-five patients received cycles including 50 mg doses in contravention of the study protocol. The average administered dose for all study patients was 96.7 mg. Two hundred and sixty-four patients (40%) received only replacement cycles throughout the study. The majority of those patients, 231 individuals (87.5%), received only one complete replacement cycle. Thirty-three patients (12.5%) received 2 or more replacement cycles of iron sucrose. Only maintenance therapy was given to 320 patients (48.1%). Of the patients receiving only maintenance regimens, 246 (76.9%) received one cycle, while 74 patients (23.1%) received 2 or more cycles. Eighty-one patients (12%) received both replacement and maintenance cycles.

Adverse events

Drug-related events. Six hundred sixty-five patients were administered a total of 8583 doses of iron sucrose throughout the study. There were no drug-related serious adverse events or deaths associated with iron sucrose. There were 29 nonserious drug-related events reported in 21 patients, yielding a nonserious adverse drug event (ADE) per-patient incidence of 4.4%, and a per-exposure incidence of 0.34%. Taste disturbance occurred in 0.13% of exposures and 0.17% of patients. Excluding taste disturbance, the nonserious ADE per-patient incidence was 2.7%, and the per-exposure incidence was 0.2%. The incidence of nonserious drug-related adverse events associated with administration of 50 mg doses did not differ significantly compared to those associated with 100 mg doses. A complete list of drug-related nonserious adverse events is presented in Table 3. Two patients, one who complained of pruritus on the days of the tenth replacement dose and first maintenance dose, and one who complained of constipation which preceded the fourth maintenance dose and persisted 10 days, were withdrawn from the study because of nonserious adverse events which their investigators considered related to study drug. These two

Table 3. Nonserious adverse drug events (ADE)[a]

Description	#Events	Severity			Incidence	
		Mild	Moderate	Severe	Per exposure[b]	Per patient[c]
Constipation	3	1	1	1	0.00035	0.0045
Hypotension	3	0	3	0	0.00035	0.0045
Pruritis	2	2	0	0	0.00023	0.0030
Vomiting	3	0	3	0	0.00035	0.0045
Transaminase elevation	1	0	1	0	0.00012	0.0015
Dermatitis	1	1	0	0	0.00012	0.0015
Diarrhea	1	0	1	0	0.00012	0.0015
Dizziness	1	1	0	0	0.00012	0.0015
Dry mouth	1	1	0	0	0.00012	0.0015
Nausea	2	0	2	0	0.00023	0.0030
Subtotals	18	6	1	0	0.00211	0.027
Taste disturbance	11	10	1	0	0.00128	0.0165
Totals	29	16	12	1	0.00339	0.0436

[a]Serious ADE = 0; [b]8583 total doses; [c]665 total patients; 5 had more than 1 event.

patients were not listed as drug intolerant and were not precluded from further therapy.

Unrelated adverse events. The most common unrelated severe adverse events in this study were congestive heart failure (12 patients; 1.8%), sepsis (11 patients; 1.7%), myocardial infarction (8 patients; 1.2%), chest pain, pneumonia, pulmonary edema, and cerebrovascular accident (7 patients each; 1.1% respectively).

Death and infection. Fifty-four patients required hospitalization for infection (226 hospitalizations per 1000 patient years). None of these events was considered related to the study drug. Twenty-eight study patients died during the study period (mean duration 101 days, range 9 to 439 days) and a safety-reporting follow-up period (30 days after the last dose of iron sucrose). Five deaths were thought to be the result of infection (estimated 21 deaths/1000 patient years). No deaths were deemed to be related to iron administration by the treating physician.

The mortality rate from infection or sepsis of 21 deaths per 1000 patient years was not significantly different from the rate of 34.2 deaths per 1000 patient years observed by the USRDS [2] among all hemodialysis patients reported from 1995 through 1997 (relative risk $21/34.2 = 0.61$, $P = 0.08$) (Fig. 1). The hospitalization rate from infection of 226.5 hospital admissions per 1000 patient years was significantly lower than that the rate of 422 hospitalizations for infection per 1000 patient years observed by the USRDS for all hemodialysis patients (relative risk $226.5/422 = 0.54$, $P < 0.001$) (Fig. 1) [4].

Hypersensitivity reactions. There were no drug-related hypersensitivity reactions (anaphylactic or allergic reactions) in this study. One patient experienced anaphylactic reaction to new dialysis tubing, unrelated to the study drug. The patient continued in the study after the event, received the remaining doses of the iron sucrose regimen without incident and successfully completed the study.

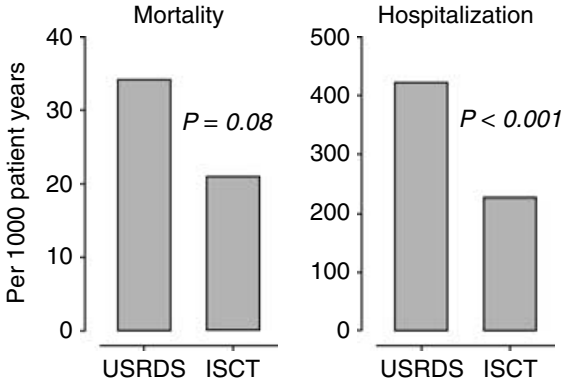

Fig. 1. Relative risk of mortality or hospitalization due to infection in patients receiving iron sucrose in the Iron Sucrose Clinical Trial (ISCT) compared to that observed among all United States hemodialysis patients (USRDS). Rates of infection-related mortality and hospitalization in ISCT patients compared favorably with those in the general USRDS population.

DISCUSSION

We report the results of a large, multiple-dose clinical trial to determine the safety of iv iron sucrose for iron replacement, iron maintenance, or both in patients undergoing chronic hemodialysis. We examined the safety of iron sucrose in a large cohort of hemodialysis patients under conditions of repeated iron replacement and/or maintenance administration that closely mimic the clinical situation. The regimens adhered closely to published K/DOQI criteria.

Iron sucrose administration was associated with no serious drug-related adverse events. Thus, among 665 patients collectively administered over 8500 doses of iron sucrose we found no serious ADE and no drug intolerance. Since 98% of the patients in this study had not previously been exposed to iron sucrose, we calculated the per-patient and per-exposure incidence of

non-serious ADE to be 4.4% and 0.34%, respectively. Taste disturbance accounted for the majority of ADEs, was mild, did not tend to recur on readministration, and did not preclude further iron sucrose administration. Excluding taste disturbance, the nonserious per patient ADE rate was 2.7% and per exposure nonserious ADE rate 0.2%. The observed rate of nonserious drug-related hypotension (0.0004% of exposures and 0.004% of patients) was consistent with previous findings in smaller studies showing no drug-related hypotension. No patient with prior iron sensitivity to either iron dextran, ferric gluconate, or both experienced a serious ADE.

These observations are consistent with previous studies of iron sucrose [6, 19]. However, comparing these safety results to those obtained with other available iv iron agents requires great caution. Clinical trials directly comparing safety of iv iron agents have not been performed. Thus, explicit comparisons between agents have involved use of historical controls [16]. The historical literature on safety of iv iron agents, however, frequently lacks information crucial to assessment of safety, including the number of doses administered, dose size, and rate of administration, whether patients were incident (not previously exposed) or prevalent, detailed descriptions of reactions, information on timing of reactions, distinctions between serious (life-threatening or requiring therapeutic intervention) and nonserious adverse reactions, and definitions of drug intolerance. In a recent report, for example, four iron dextran historical control studies were used to compare reaction rates observed in patients after a noniron dextran agent given 125 mg iv over 10 minutes [16]. One of the control studies referred to unpublished information on a dextran-coated iron hydroxide (Feridex®; Advanced Magnetics, Inc., Cambridge, MA, USA; and Werner Stricker AG, Zollikofen, Switzerland) used as an MRI contrast agent and lacking published safety data at any dose [18]. A second study was limited to information on Imferon® (Fisons, Loughborough, UK), an iv iron dextran unavailable since 1991, administered primarily at doses of 250 to 500 mg in patients without renal disease [14]. A third study was a retrospective trial lacking information on number of iron doses administered [10]. The fourth, lacking direct information on number of iron dextran doses administered, dose sizes or rate of administration, or the number of patients treated, relied on "reasonably accurate" commercial sales information and voluntary reporting of allergic or anaphylactic events to the World Health Organization [8].

More complete information on serious ADE after iron dextran and ferric gluconate are, however, available. A retrospective analysis of a United States dialysis provider database yielded 165 suspected serious ADEs after 841,252 iron dextran doses, for a per-exposure serious ADE rate of 0.02% [11]. A second retrospective analysis of a United States dialysis provider database (1,066,099 iron dextran doses in 48,509 patients) found that iron dextran–associated life-threatening reactions, identified as those requiring resuscitative medications, were limited to incident patients receiving a test dose or first therapeutic dose [abstract; Walters BAJ, Van Wyck DB, *J Am Soc Nephrol* 12:418A, 2001]. Ferric gluconate ADE rates have been examined prospectively in 2534 incident (ferric gluconate naive) hemodialysis patients administered a single 125 mg dose iv over 10 minutes [7]. A single life-threatening reaction was seen in one patient (per-exposure and per-patient serious ADE rate 0.04%), and drug intolerance was seen in 11 patients (drug intolerance per-exposure and per-patient ADE rate 0.44%). Other reports assessing ADE rates after ferric gluconate are from studies in which the patient enrollment was much smaller [17], or the administered doses were larger (≥250 mg) [12]. Information in patients given repeated doses of ferric gluconate under replacement and maintenance regimens in hemodialysis patients is not, to our knowledge, available.

Given the foregoing serious ADE rates reported for iron dextran and iron sucrose, we performed post hoc power tests to shed light on whether the current study was sufficiently large enough to identify low-probability adverse events. Post hoc calculations confirmed that if the serious per-person ADE rate or the drug intolerance ADE rate in the affected population had been 0.6%, 0.4%, or 0.2%, the probability that one or more serious reactions would have been encountered was 98% or greater, 93% or greater, or 74% or greater, respectively.

Despite the results of prospective, multicenter trials showing no relationship between iron dosing or body iron status and bacteremia in dialysis patients, a biologically plausible relationship exists between all parenteral iron treatment and infection [9, 15]. In the current study, we found that the mortality rate from infection or sepsis among patients of undergoing iron sucrose therapy compared favorably with that of the overall United States hemodialysis population. We also found that the hospitalization rate from infection among patients receiving iron sucrose was significantly lower than that of the general United States hemodialysis population. Differences in patient selection limited interpretation of these results, however. Patients in the current clinical trial were likely healthier at enrollment than are patients in the general United States dialysis population. On the other hand, although 100% of patients in the trial were exposed to iv iron, only 55% to 60% of patients in the general population received iv iron during the course of a year [2, 4]. Nevertheless, our findings are in keeping with those of a recent large, multicenter anemia trial [13], in which hemodialysis patients randomized to normal compared to subnormal hemoglobin targets required higher doses of iv iron sucrose but suffered no increase in mortality. Moreover, regardless of hemoglobin target, there was no

difference in iron sucrose dose between survivors and nonsurvivors.

CONCLUSION

This study demonstrates that iron sucrose is safe in the treatment of iron deficiency and the maintenance of adequate iron stores in EPO-treated dialysis patients, including those sensitive to iron dextran, ferric gluconate, or both.

APPENDIX

Additional members of the Iron Sucrose (Venofer®) Clinical Trials Group: Louis Ardon (Montgomery, AL); Mario Belledonne (Silver Spring, MD); Dinesh Chatoth (University of Arkansas, Little Rock, AR); Thomas Crouch (Kansas City, MO); Piotr Tadeusz Dyk (Wentzville, MO); John Elder (Santa Barbara, CA); Danny Fischer (Cincinnati, OH); Leland Garrett (Raleigh, NC); Michael Germain (West Springfield, MA); Carl Goldstein (Mountainside, NJ); Marvin Greiff (Rochester, NY); Joseph Guzzo (Allentown, PA) Sally Hood (Methuen, MA); Nathan Levin (New York, NY); Jim Lewis (Birmingham, AL); Norman Lunde (Arden Hills, MN); Edwin Macon (Emory University, Atlanta, GA); Nawar Mansour (Memphis, TN); Kevin McConnell (Charlottesville, VA); Mary Meyer (Oregon Health Sciences University, Portland, OR); Ellen Morrissey (San Pablo, CA); Ramakant Mulay (Dyersburg, TN); Jesus Navarro (Tampa, FL); Clyde Pence (Pensacola, FL); Russell Pikus (Columbus, IN); John Rastall (Vancouver, WA); Denise Ricker (El Cerrito, CA); Allan Schwartz (Hahnemann University, Philadelphia, PA); Warren Shapiro (Brooklyn, NY); Jeffrey Silberzweig (The Rogosin Institute, Woodside, NY); James Sterrett (Paterson, NJ); Stephen Thomsen (Union City, NJ); James Van Gelder (Hollywood, FL); Geoffrey Walker (Irving, TX); Duane Wombolt (Norfolk, VA); Thomas Wooldridge (Tupelo, MS); Elaine Worcester (University of Chicago, Chicago, IL); and Steven Zelman (Mt. Vernon, IL).

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