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CLINICAL STUDY

Safety of total dose iron dextran infusion in geriatric patients with chronic kidney disease and iron deficiency anemia

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Abstract

There are limited data on total dose infusion (TDI) using iron dextran in geriatric chronic kidney disease (CKD) patients with iron-deficiency anemia (IDA). Our goal was to evaluate the safety of TDI in this setting. We conducted a retrospective chart review spanning a 5 year period (2002–2007), including all patients with CKD and IDA who were treated with iron dextran TDI. Patient demographics were noted, and laboratory values for creatinine, hemoglobin and iron stores were recorded pre- and post-dose. TDI diluted in normal saline was administered intravenously over 4-6 hours after an initial test dose. One hundred fifty-three patients received a total of 250 doses of TDI (mean ± SD = 971 ± 175 mg); age was 69 ± 12 years and creatinine 3.3 ± 1.9 mg/dL. All stages of CKD were represented (stage 4 commonest). Hemoglobin and iron stores improved post-TDI ($P < 0.001$). None of the patients experienced an anaphylactic reaction or death. Adverse events (AEs) were noted in 8 out of 250 administered doses (3.2%). The most common AEs were itching, chills and back pain. One hundred and ten doses of high molecular weight (HMW) iron dextran produced 6 AEs (5.45%), whereas 140 doses of low molecular weight (LMW) iron dextran produced 2 AEs (1.43%), a non-significant trend ($P = 0.1433$ by Fishers Exact Test). Iron dextran TDI is relatively safe and effective in correcting IDA in geriatric CKD patients. Fewer AEs were noted with the LMW compared to the HMW product. LMW iron dextran given as TDI can save both cost and time, helping to alleviate issues of non-compliance and patient scheduling.

Keywords

Chronic kidney disease, geriatrics, iron deficiency anemia, iron dextran, safety, total dose iron

History

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Introduction

Intravenous (IV) iron remains a fundamental component of the treatment of anemia in chronic kidney disease (CKD) patients and is crucial to achieving target hemoglobin levels.[1,2] It has thus become a cornerstone of therapy for anemia in chronic kidney disease (CKD) – for both dialysis-dependent and non-dialysis dependent CKD. Benefits of maintaining a target goal (which itself has changed over the last few years) include significant improvements in cardiac physiology and quality of life.

One of the earliest IV compounds used to treat iron deficiency anemia was iron dextran (ID). Its popularity as a first-line agent has waned considerably over time, due to concerns regarding safety as well as newer compounds becoming available on the market.[3,4] A review of previous data as well as economic considerations might prompt the clinician to re-examine the merits of ID. There still remains the advantage of single dose therapy with intravenous iron dextran, thereby assuring compliance with prescribed therapy, minimizing inconvenience to patients and reducing cost of care to the provider. Single dose therapy with ID is hence advantageous to patients and providers, and its safety with regard to total dose infusion (TDI) in dialysis patients has been established.[5] No other IV iron preparation affords this dosing opportunity. The newer iron formulations, though reportedly associated with less adverse effects, are substantially more expensive and require multiple office visits.[6,7] In light of the Medicare bundled reimbursement system for dialysis drugs and services, clinicians have an added incentive to review efficacy, cost and safety issues relating to the treatment of IDA.[8]

Iron dextran is still being used as the preferred product in some centers in the public sector, barring documented allergy to the compound. There is limited data on total dose infusion, using iron dextran given as a single bolus, in non-dialysis dependent CKD patients with iron-deficiency anemia (IDA). Our goal was to evaluate the safety of iron dextran TDI in this setting. We also sought to compare the safety of the two types of ID that have been commercially available – low molecular weight versus high molecular weight iron dextran.

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Patients and methods

The study was conducted at the Overton Brooks VA Medical Center in Shreveport, Louisiana. Approval was obtained from our institutional review board and research and development committees. We conducted a retrospective chart review spanning a 5-year-period (2002–2007), including all patients with chronic kidney disease and iron-deficiency anemia who were treated with iron dextran total dose infusion (TDI) at our medical center during that time-frame. It should be noted that at our medical center, iron dextran was one of the first-line IV iron agents on the formulary in the years under study. The then prevailing KDOQI practice guidelines for treatment of anemia in CKD patients were followed in the clinical care of these patients, regarding use of both erythropoiesis stimulating agents and intravenous iron.

Iron dextran TDI diluted in normal saline was administered intravenously (IV) over 4–6 hours (if there was no reaction to an initial test dose of 25 mg). Patient demographics and comorbid conditions were noted, and laboratory values for creatinine, hemoglobin (Hgb), hematocrit (Hct), serum iron (Fe), % transferrin saturation (Tsat) and ferritin (Ftn) were recorded pre-dose and post-dose. The post-dose values were measured 10–120 days post-infusion, when the patient came back to the clinic or hospital for follow-up care.

The efficacy data was analyzed using Student's *t*-test to compare mean values. Safety comparisons between the low and high molecular weight products were made using Fisher's Exact Test. Microsoft Excel version 2007 was used to perform the above statistical testing (Microsoft Corporation, Redmond, WA).

Results

Over the 5-year study period (2002–2007), 153 patients received a total of 250 doses of TDI (mean ± SD = 971 ± 175 mg). The patients' mean age was 69 ± 12 years, and the mean serum creatinine at enrollment was 3.3 ± 1.9 mg/dL. All stages of CKD were represented – see Table 1. Stage 4 CKD was the commonest, being present in 37% of the study population, followed by stage 3 that was noted in 31%. Of note, 18% of the population comprised of patients on dialysis.

Efficacy results indicated that Hemoglobin and Fe stores improved post-TDI with iron dextran ($P < 0.001$) – as depicted in Table 2.

In our study, Adverse Events (AEs) were noted in 8 out of a total of 250 administered doses. This yielded a total adverse event rate of 3.2% per episode of IV iron dextran infusion. Table 3 lists the details of the AE's that were recorded. The commonest AEs were itching, chills and back pain. No anaphylactic reactions were noted. None of the 8 episodes of AE required the affected patients to need Emergency Room evaluation, outpatient observation or hospitalization. During the 5-year study period, neither deaths nor life-threatening complications resulting from TDI administration were noted.

We stratified the data by the molecular weight of the iron dextran that was administered (low vs. high). We found that 110 doses of high molecular weight (HMW) iron dextran (trade name Dexferrum) produced a total of 6 episodes of AEs. On the other hand, 140 doses of low molecular weight (LMW) iron dextran (trade name INFeD) produced 2 episodes of AEs. When expressed as total adverse event rate per episode of IV infusion, this led to the HMW product having a higher rate than the LMW product, 5.45% versus 1.43%, respectively. The trend, however, was not statistically significant ($P = 0.1433$ by Fishers Exact Test) – as noted in Table 4.

Table 1. Distribution of IV iron dextran doses by CKD stage.

CKD Stage	Number of doses	Percent of total
CKD 1	2	1%
CKD 2	2	1%
CKD 3	77	31%
CKD 4	92	37%
CKD 5	33	13%
CKD 6 (on dialysis)	44	18%
Total	250	100%

Table 2. Effect of iron dextran TDI on hemoglobin, hematocrit and iron stores.

	Hgb (g/dL)	Hct (%)	Fe (mcg/dL)	TIBC (mcg/dL)	Tsat (%)	Ftn (ng/mL)
Pre-TDI	10.8 ± 1.4	32.5 ± 4.3	42 ± 18	292	15 ± 6	183 ± 228
Post-TDI	11.3 ± 1.5	33.9 ± 4.7	62 ± 28	259	24 ± 10	436 ± 281
p-Value	≪0.001	≪0.001	≪0.001	<0.00001	≪0.001	≪0.001

Abbreviations: Hgb, hemoglobin; Hct, hematocrit; Fe, serum iron; TIBC, total iron binding capacity; Tsat, transferrin saturation; Ftn, serum ferritin; TDI, total dose infusion with iron dextran.

Table 3. Adverse events with IV iron dextran total dose infusion.

Adverse event	Number of events
Itching	4
Back pain	2
Chills	2
Nausea	1
Tongue swelling	1
Rash	1
Urticaria	1
Flushing	1
Increased BP	1
Diaphoresis	1
Restlessness	1
Anaphylactic reactions	0
Death	0

Table 4. Adverse events with the different preparations of intravenous iron dextran, expressed as a percentage.

	LMW	HMW
Adverse events absent	98.6	94.5
Adverse events present	1.4	5.5

Note: $P = 0.1433$ by Fishers Exact Test.
Abbreviations: LMW, low molecular weight iron dextran; HMW, high molecular weight iron dextran.

Discussion

The study population comprised essentially of geriatric patients (veterans) with CKD and iron deficiency anemia – the patients' mean age being 69 ± 12 years. It adds to the body

of medical literature, which currently has a paucity of studies using IV iron total dose infusion performed on this group. Our results clearly indicate a significant benefit to patients with the use of IV dextran in terms of improvement of both iron stores and hemoglobin.

Data on the use of IV iron preparations to treat IDA continues to proliferate in the literature. However, few large trials provide a head to head comparison between products, and even fewer are conducted without the support of pharmaceutical companies. Until larger, randomized, controlled and blinded trials are published, it may be beneficial to revisit older modalities of treatment, albeit with strict monitoring for any adverse effects. It is pertinent to point out that our study had no influence from any pharmaceutical company. It does carry the usual inherent weaknesses of any retrospective study. However, its nature as a study performed at a single-center – that followed a set protocol for administration of IV iron – removed the effect of inter-operator variability often seen with retrospective data collection involving multiple centers with differing protocols.

The reputation of iron dextran (ID) as an unsafe agent may be outdated, but continues to overshadow its effectiveness as a therapeutic agent in the treatment of iron deficiency anemia (IDA). Yee et al.[9] noted after a review of clinical databases that the incidence of anaphylactoid reactions reported for iron dextran is less than previously reported. However, iron dextran continues to be labeled as the agent with the most associated adverse events.[10] On occasion, ID is touted for its cost benefit and even its superiority as being less nephrotoxic compared to the other iron formulations.[11] Our retrospective study and chart review of total dose infusion of iron dextran revealed few adverse events overall, and no serious adverse events. Not a single event of anaphylaxis, anaphylactoid reaction or death was recorded through the course of this study, which was conducted over a 5-year period of time.

Another study published in 2007 by Sav et al.,[12] comparing low molecular weight iron dextran with iron sucrose, demonstrated equal efficacy and a comparable adverse effect profile. A recent study in India, a setting where availability of resources plays a vital role in disease management, compared all three preparations (low molecular weight iron dextran, iron sucrose, and sodium ferric gluconate complex), and found no significant difference between the three groups in terms of non-serious adverse events.[13]

Chertow et al.[14] have shown that while the non-dextran iron formulations appear to be associated with somewhat lower AE rates (compared to low molecular weight iron dextran), overall AE rates are exceptionally low. As a result, the cost per adverse event prevented is extraordinarily high, estimated at approximately $5.0–7.8 million, and the cost per death prevented considerably higher, namely $33 million. In most medical fields, this would not be considered as being cost-effective.[15] The authors[14] also calculated that use of iron sucrose rather than low molecular weight iron dextran in the United States dialysis population would result in nearly $210 million higher in costs to the ESRD program.

There were no deaths related to TDI iron dextran in our study. Only 8 out of 250 doses (3.2%) were associated with adverse events – none of which were life threatening. Of these 8 AE's, 4 occurred in patients with CKD Stage 3, and 2 each in patients with CKD stages 4 and 5. Six of the doses associated with adverse events occurred with the use of high molecular weight iron dextran; 2 occurred with the low molecular weight product. When expressed as total AE event rate per episode of IV infusion, this led to the HMW product having a higher rate than the LMW product, 5.45% versus 1.43%, respectively. This finding supports previously reported data (mainly from the field of Oncology) on the higher risks associated with the HMW preparation[16,17]. In fact, LMW ID has been shown to be equally effective and as safe as iron sucrose and ferric gluconate in treating chemotherapy patients with small frequent doses.[17] Our study confirms that in the setting of IDA in CKD, when given as a *total dose infusion*, the LMW preparation reduces the incidence of adverse events as compared to the use of HMW ID.

Our adverse event rate using iron dextran TDI is similar to that observed in other studies performed with iron dextran. Fishbane conducted a retrospective chart review of 573 hemodialysis patients treated with IV iron dextran (INFeD) over a 2-year period – though these were not TDI. Twenty-seven patients (4.7%) had adverse reactions. Four patients (0.7%) had reactions classified as serious.[18]

The importance of treating iron deficiency anemia has drawn even greater attention in the era of the bundled reimbursement system for dialysis drugs and services.[19] Erythropoiesis-stimulating agents (ESAs) are Medicare's largest drug expenditure for CKD patients. Lowering ESA dosages through effective iron replacement has been established[20] and will likely continue as an effective economic stratagem. Iron dextran was the first IV iron preparation shown, back in the mid-1990's, to lower the erythropoietin doses needed for effective anemia management.[21]

Despite growing emphasis on the management of the multitude of complications that arise secondary to kidney disease, the implementation of treatment guidelines remains challenging. Non-compliance by patients and cost of care remain formidable hurdles for physicians practicing in virtually every clinical setting. The infrequent use of IV iron in patients with CKD may be explained in part by the need for multiple clinic visits;[22] this in turn often results in lower hemoglobin levels in patients starting on dialysis, with its deleterious cardiovascular (and other) consequences in ESRD patients. Intravenous iron dextran given as a single, total dose infusion is easier and more convenient to the patient as well as to the clinician and his practice, thereby improving patient compliance – which is important in a bundled reimbursement system with penalties imposed for clinical targets not being met.

In the last four years, two new formulations of intravenous iron have been introduced into the US market. Ferumoxytol received FDA approval in June 2009 and is marketed under the trade name Feraheme®; it is currently the most expensive IV iron formulation on the US market that has an established ASP (average sales price) pricing. However, its largest approved single dose is 510 mg; this would still require the average adult patient to receive at least two doses for repletion of total body iron stores. In clinical studies,[23–25] hypotension was reported in 1.9% (33/1726) of subjects receiving Feraheme, including three patients with serious hypotensive reactions. Serious hypersensitivity reactions were reported in

0.2% (3/1726) of patients. Post-marketing data in 18 months subsequent to the drug's introduction in the United States in July 2009 revealed that 40 serious adverse events were reported. This represents a rate of 0.1 percent of the 35,000 ''patient exposures'' reported.

In late July 2013, ferric carboxymaltose injection (marketed in the US as Injectafer®) received FDA approval for the treatment of iron deficiency anemia in adult patients who have intolerance to oral iron or have had an unsatisfactory response to oral iron. It also received an indication for use in iron deficiency anemia in adult patients with non-dialysis dependent chronic kidney disease (NND-CKD). Treatment-related adverse events were significantly fewer with ferric carboxymaltose than with oral iron (2.7% and 26.2%, respectively; $P < 0.0001$).[26] However, it should be noted that this drug has just been introduced into the market, and there is little post-marketing experience at this point. The AE rate may go up with greater use and the passage of time.

Table 5 lists the Average Sales Price (ASP) of the currently available IV iron products. At the time of going to press, the ASP of ferric carboxymaltose is still to be determined, having been introduced less than 6 months prior. As can be readily noted, iron dextran has the lowest price of all the available products. It should also be noted that only iron dextran has been consistently used as a total dose infusion, whereas the newer agents are used in much smaller doses that require frequent administration.

The IV iron products reflect only part of the costs incurred in treating iron deficiency anemia. In addition to the medications, the health care system has to bear several other indirect costs. These are enumerated in detail in Table 6, and involve the cost of personnel, equipment, IV fluids and travel. Opportunity costs to the physician practice also have to be considered. For iron deficient geriatric patients with CKD, their providers and the health care system overall, iron dextran may regain momentum as a practical and safe approach to addressing these issues. Thus, the problems of both cost and compliance could be ameliorated to some extent by returning to the older and less expensive alternative of iron dextran.

Finally, the non-dextran forms of intravenous iron have been reported to carry a greater risk of causing events such as proteinuria, oxidative stress, endothelial dysfunction and inflammation.[27–30] This would constitute another argument for using iron dextran over the non-dextran alternatives.

Table 5. Prices (in USD) of intravenous iron products, as of November 2013.

	AWP* (per mg)	ASP** (per mg)
Iron sucrose (Venofer)	0.60	0.272
Sodium ferric gluconate (Ferrlecit)	0.38	0.232
Iron dextran (InFed)	0.38	0.243
Iron dextran (Dexferrum)	0.45	0.243
Ferumoxytol (Feraheme)	1.14	0.681

Note: *Average Wholesale Price, according to McKesson Drugs.
**Average Sales Price, effective October 1, 2013 through December 31, 2013.

Table 6. Costs incurred on IV iron products.

To the Clinic
- Personnel (nursing, receptionist, scheduler, biller & coder, etc.)
- IV Iron medication itself
- Equipment (needles, cannulae, tubing sets)
- Fluids (normal saline)
- Time (electricity, rent, etc.)
- Increased risk for medical errors with each additional encounter

To the Patient
- Travel costs
- Sick time may not be ''paid'' leave for workers paid hourly wages
- Increased exposure to pain, invasive procedures and nosocomial infections

To Physician revenue
- Room occupied for 30–60 minutes (vs. revenue from seeing new or follow-up patients)

Conclusions

The total adverse event rate was 3.2% per episode of IV iron dextran infusion. Low molecular weight iron dextran seems to reduce the rate of adverse events, compared to the high molecular weight preparation, when used for the treatment of iron deficiency anemia in geriatric chronic kidney disease patients. No deaths, anaphylactic reactions or life threatening events were observed in this study with either formulation (LMW or HMW ID). The use of total dose infusion, using LMW iron dextran given as a single bolus, may compare favorably with other IV iron products in terms of both efficacy and side-effect profile. It confers the additional advantages of both convenience to the patient and reduced cost to the provider and the health care system.

Declaration of interest

None of the authors has any financial conflict to disclose.

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