Adverse Events with IV iron

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Disclosures

- I have no financial disclosures

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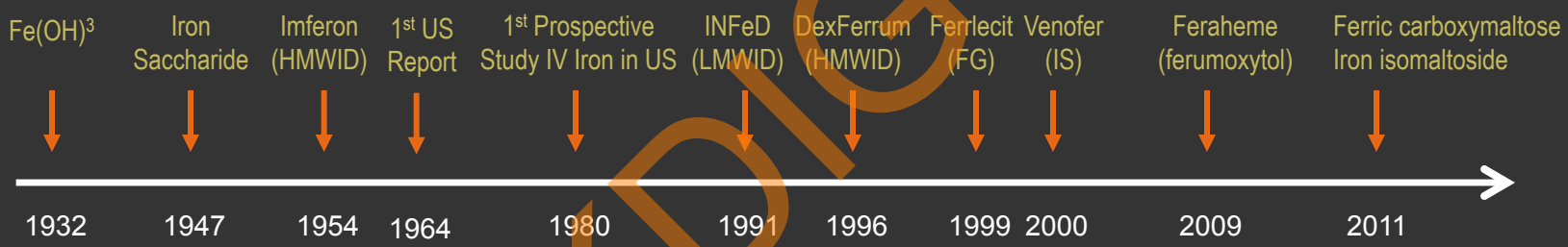
- This presentation contains published studies of unapproved methods of administration

IN GOD WE TRUST, ALL

History of IV Iron



FDA-approved Indications

Agent	FDA-approved Indications
Ferric gluconate[1]	Adult and pediatric HD patients aged 6 years and older receiving ESAs
Iron sucrose[2]	Dialysis-dependent patients with CKD receiving ESAs
	Nondialysis-dependent patients with CKD receiving or not receiving ESAs
Iron dextran[3-4]	Patients with documented iron deficiency in whom oral iron administration is unsatisfactory or impossible
Ferumoxytol[5]	Iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with CKD
Ferric carboxymaltose[6]	Patients with documented iron deficiency in whom oral iron administration is unsatisfactory or impossible
	Iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with CKD

CKD = chronic kidney disease. ESA = erythropoiesis-stimulating agent. HD = hemodialysis.

1. Ferrlecit. Available at: http://www.products.sanofi-aventis.us/ferrlecit/ferrlecit.pdf. Accessed October 3, 2013.
2. Venofer. Available at: http://www.venofer.com/PDF/Venofer_IN2340_Rev_9_2012.pdf. Accessed October 3, 2013.
3. INFeD Available at: http://pi.actavis.com/data_stream.asp?product_group=1251&p=pi&language=E. Accessed October 3, 2013.
4. Dexferrum. Available at: http://www.americanregent.com/documents/Product16PrescribingInformation.pdf. Accessed October 3, 2013.
5. Feraheme. Available at: http://www.feraheme.com/downloads/feraheme-pi.pdf. Accessed October 3, 2013.
6. Injectafer. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203565s000lbl.pdf. Accessed October 3, 2013.

IV Iron Dosing

Formulation	Approved Dosing	Maximum Safe Dose
Ferric gluconate	125mg over 10-60 min	250mg over 1 hour[1]
Iron sucrose	100-400mg over 2-90 min	300mg over 2 hour[2]
Iron dextrans	100mg over 2 min	TDI over 1-4 hours[3-4]
Ferumoxytol	510mg in ≤ 17 seconds	1020mg over 15 minutes[5]
Ferric carboxymaltose	750mg over 15 min	1000mg over 15 min[6]
Iron isomaltoside (Europe only)	20mg/kg over 15 min	20mg/kg over 15 min[7]

1. Folkert et al. *Am J Kidney Dis*. 2003;41:651-657.2. Chandler et al. *Am J Kidney Dis*. 2001;38:988-991. 3. Auerbach et al. *Am J Kidney Dis*. 1998;31:81-86. 4. Auerbach et al. Presented at American Society of Hematology, December 2009, New Orleans, LA. 5. Auerbach et al. Am J Heme 2013. 6. Ferinject [summary of product characteristics]. France: Vifor Pharma; 2009. 7. MonoFer [summary of product characteristics]. Denmark: Pharmacosmos; 2010.

Safety Issues

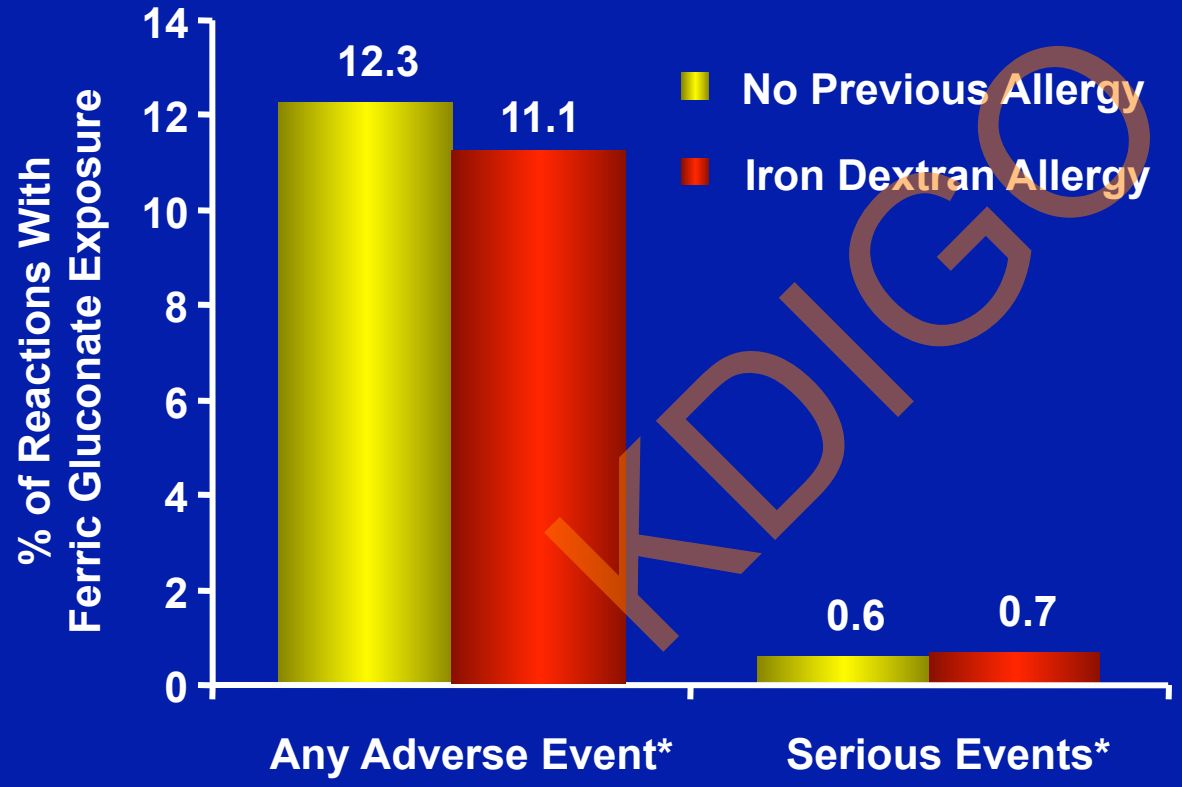
US Safety Study of Ferric Gluconate: Serious AEs vs Historical Iron Dextran Control

Event	Iron Dextrans (%, N, CI)	Ferric Gluconate (%, N, CI)	*P*
Life threatening	0.61%* 23/3768 0.36%-0.86%	0.04% 1/2493 0%-0.22%	0.0001
Drug intolerance	2.47% 64/2589 1.87%-3.07%	0.44% 11/2493 0.21%-0.71%	<0.0001

CI denotes 95% confidence interval – no overlap.
*93% reduction in risk of life-threatening reaction with ferric gluconate.

Michael et al. *Kidney Int*. 2002;61:1830-1839.

Lack of Ferric Gluconate Cross-Reactivity in Dextran-Allergic Patients



- No relationship between history of iron dextran allergy and risk for adverse events

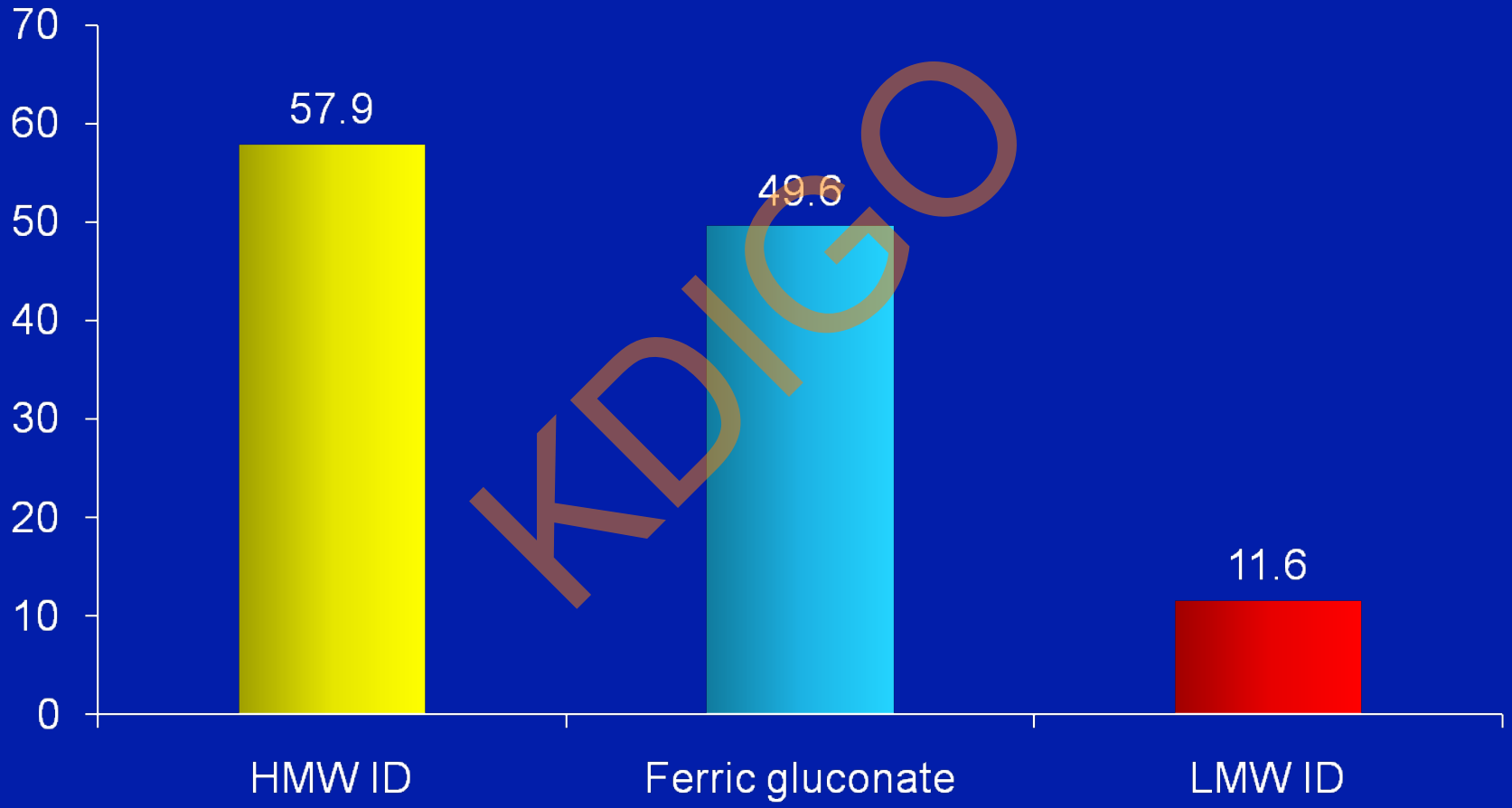
***Related or unrelated to study drug.**

Michael et al. *Kidney Int.* 2002;61:1830-1839.

As a result

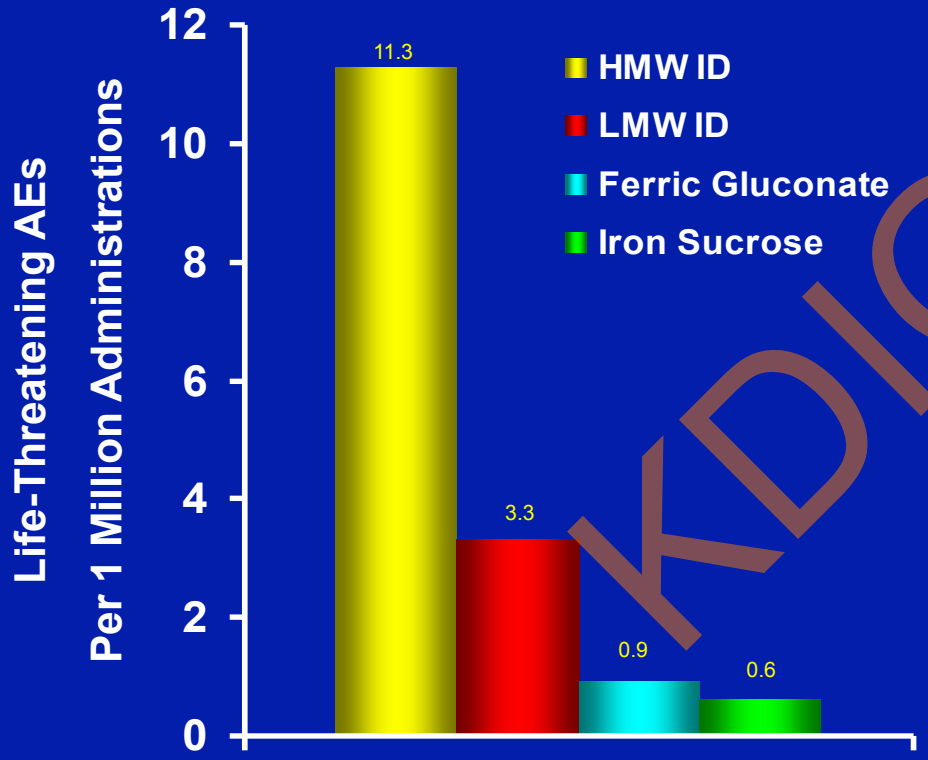
- Based on these data, overnight most dialysis patients were switched from iron dextran to ferric gluconate and later iron sucrose

Total Reported Serious AEs per Million Doses of 100mg



Chertow GM et al. *Nephrol Dial Transplant*. 2004;19:1571-1575.

AEs and IV Iron Therapy



- FDA Medwatch reports (2001-2003) show HWM ID was associated with a 3.4-fold increase in odds of life-threatening AEs
- This analysis likely underestimates AEs with HWM ID and overestimates AEs with LMW ID (All AEs reported by generic name only were attributed to LMW ID)

Chertow GM et al. *Nephrol Dial Transplant*. 2006;21:378-382.

Relative Safety of Iron Dextran (INFeD, DexFerrum, ImFeron) Preparations

- McCarthy JT, et al.
  - Adverse events in chronic hemodialysis patients receiving intravenous iron dextran--a comparison of two products. *Am J Nephrol.* 2000;20:455-62.
- Fletes R, et al.

  Suspected iron dextran-related adverse drug events in hemodialysis patients. *Am J Kidney Dis.* 2000;37:743-9.
- Chertow GM, et al.
  - Update on adverse drug events associated with parenteral iron. *Nephrol Dial Transplant.* 2006;21:378-82.
- Mamula, et al.
  - Total-dose intravenous infusion of iron dextran for iron-deficiency anemia in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 2002 Mar;34(3):286-90.
- Case, G.
  - Maintaining iron balance with total-dose infusion of intravenous iron dextran. ANNA J. 1998;25(1):65-8.
- Silverstein, et al.
  - Parenteral iron therapy options (review). *Am J Hematol.* 2004 May;76(1):74-8.
- Walters et al, NDT 2005;7:1438-1442.

AEs and IV Iron Therapy: Recent FDA Medwatch Reports

- Obtained from Freedom of Information, all AEs from 1/1/07 to 12/31/09
- Iron dextran
  - HMW ID had 116 AEs; 88 unidentifiable
  - LMW ID had 127 AEs; 75 unidentifiable
  - IMS data base: approximately five times as many doses LMW ID sold during this period

Comparative Studies

- Two prospective: LMW ID and iron sucrose[1,2]
- One metaanalysis[3]
- One prospective: Iron sucrose and ferumoxytol[4]
- One retrospective: all but HMW ID[5]
- No statistically significant difference in AEs
- One prospective FCM vs IS[6,7]

1. Monirm et al. *TATM*. 2007; 2. Sav T et al. *Ren Fail.* 2007;29:423-426. 3. Critchley et al. *TATM*. 2007; 4. MacDougall et al. *cJASN 2014 5.* Okam MM et al. *Am J Hematol*. 2012;87:E123-E124. 6. Onken et al, NDT 2013 7. Quinibi ASN 2007

FDA Review of IV Iron Anaphylactic Reactions

- IMS Database, FDA Adverse Event Reporting System, Death Certificates, ER Visits
- Reactions with all products possible
- Using current system, not possible to determine relative rates of SAE, absent head to head trials
- Spontaneous adverse event reporting cannot and should not be used for this purpose!

Wysowcki et al. *Am J Hematol*. 2010;85:650–654.

Summary of Safety of IV Irons

- AEs occur with all the formulations of IV iron
- Frequency of SAEs from prospective studies is extremely low, but current reporting mechanism tells us nothing about the frequency among available products
- Preponderance of published literature, all retrospective, suggests that HMW ID should be used only with caution
- The NCCN guidelines nJASN proscribe HMW ID and recommend LMW ID when iron is indicated for CIA

Premedication and Serious Adverse Events

- Patients SHOULD NOT be premedicated with diphenhydramine which can cause hypotension, flushing, somnolence and supraventricular tachycardia
- Inappropriate intervention can cause SAE
- Minor chest and back tightness, usually after test dose, first described by Steve Fishbane is NOT a serious AE
- Resolves without treatment: Do NOT intervene with epinephrine or diphenhydramine
- An SAE should consist of hypotension, tachypnea, tachycardia, wheezing, stridor or periorbital edema
- Premedication with steroids only for allergic diatheses

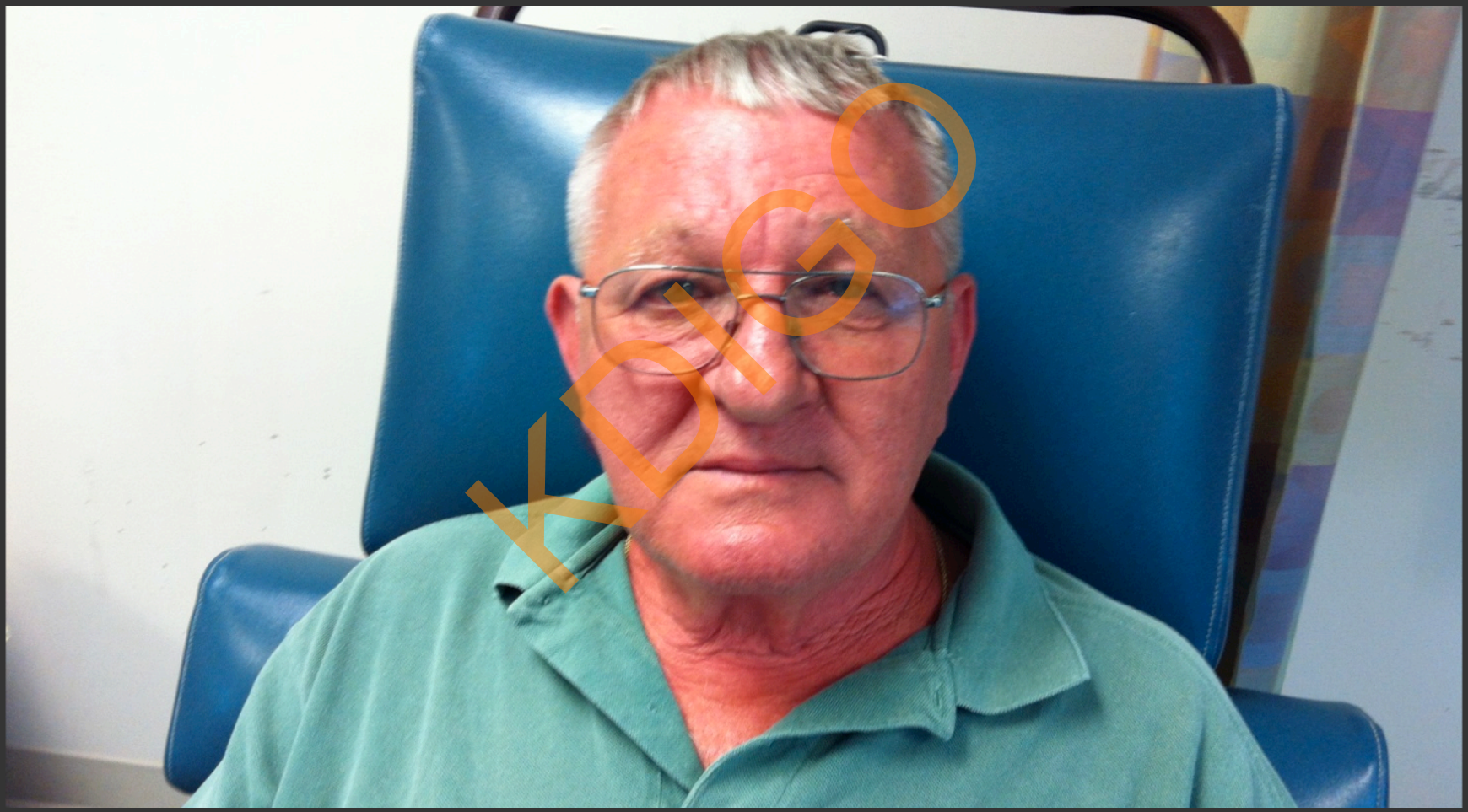
Auerbach M, Ballard H, Glaspy J. *Lancet*. 2007;369:1502-1504.

Premedication causes side effects

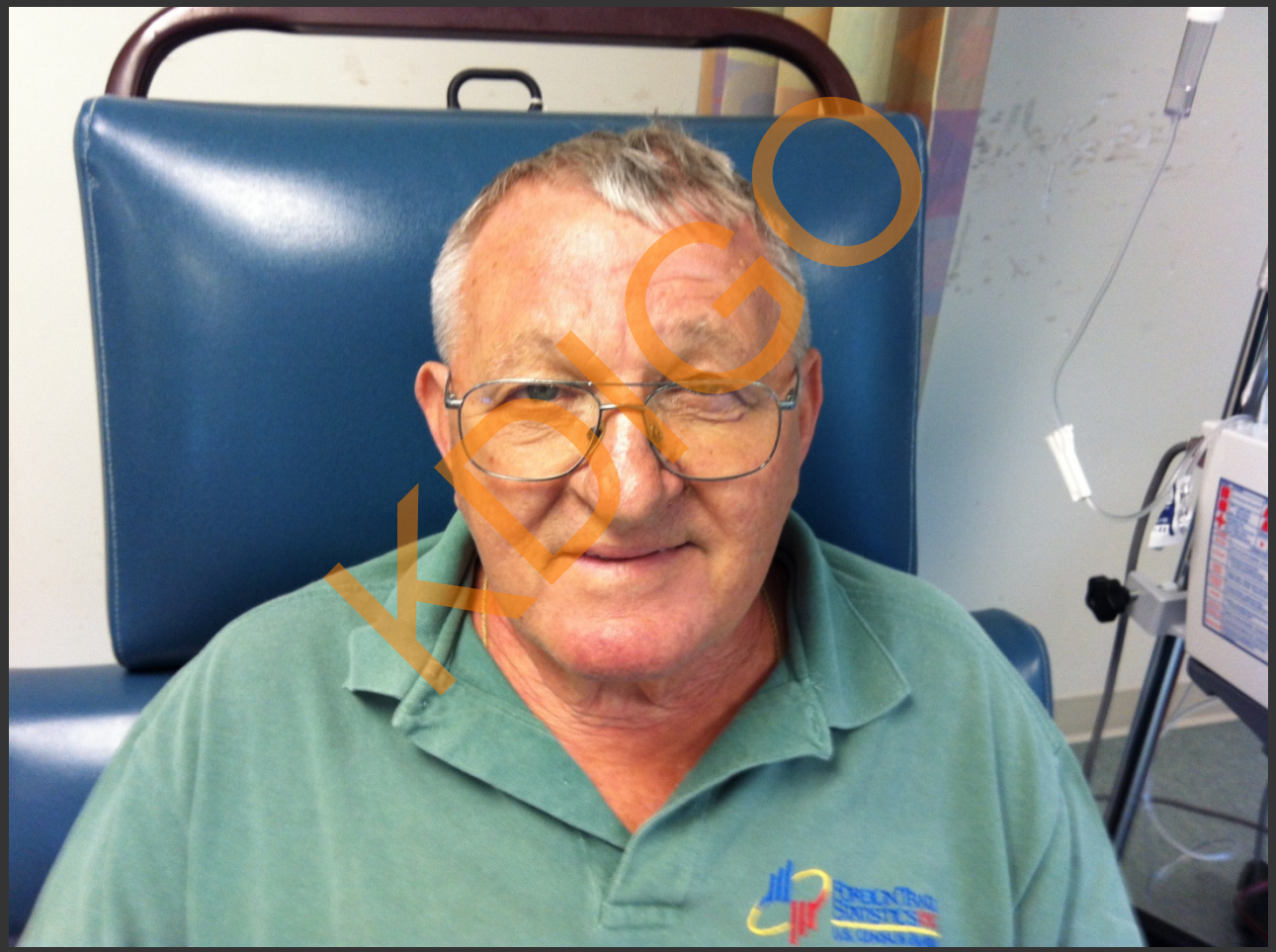
We found that 87% of the 135 patients had no reaction to iron dextran infusion. The rate of adverse reactions was substantially less than that of 25% previously reported among 481 patients who had iron deficiency due to a variety of causes (9). The most common side effect that we observed was sedation after the intravenous infusion of diphenhydramine (Parke-Davis and Warner-Lambert Co., package insert for Benadryl for injection, 1997-1998).

Barton et al; American Journal of Medicine, July 2000: Vol 109 (27-32)

Picture of a Patient with Minor Infusion Reaction to IV Iron



Picture of the Same Patient After 3.5 minutes with Infusion Reaction Resolved



HYPERSENSITIVITY FROM IV IRON DUE TO IMMUNE REACTION

- Immediate:
- Skin: Pruritis, extended flush, urticaria, angioedema
  Respiratory: Dyspnea, tachypnea, cough, bronchospasm, stridor
  GI: Nausea, emesis, colic, diarrhea
  CV: Hypo & Hypertension, tachy & bradycardia, palpitations, chest pain, shock
  CNS: Dizziness, syncope, LOC
- Delayed:
- Fever
  Arthralgia, Myalgia
  Lymphadenopathy
  Exanthems

Farnham et al, Int Archives of Allergy and Immuno 2012, Hoigne et al, Schweiz Med Wochenshr 1998

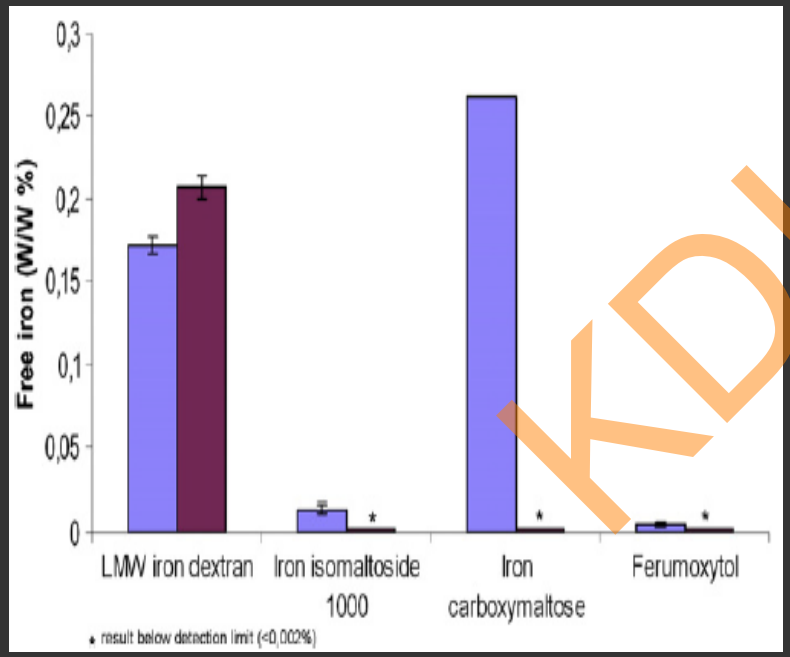
IV Iron Symptoms Due to Free Iron Toxicity

- Transient facial flushing
- Chest oppression
- Headache
- Nausea, Diarrhea, Metallic taste
- Back Pain
- Low grade fever
- Arthralgia, Myalgia

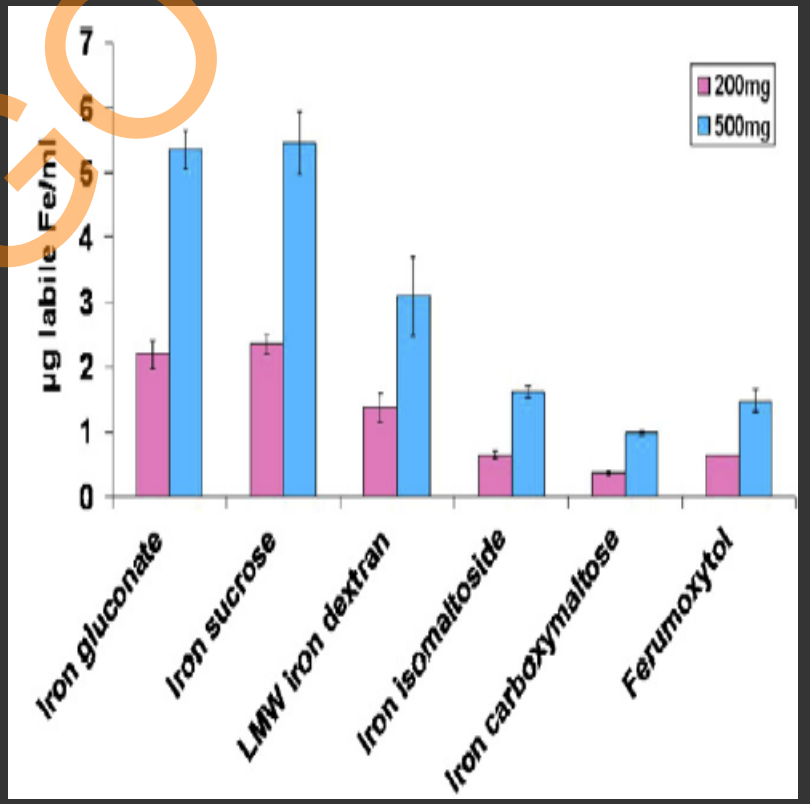
- Farnham et al, Int Archives of Allergy and Immuno 2012, Hoigne et al, Schweiz Med Wochenshr 1998

Comparison of Free and Labile Iron Content in Parenteral Iron Products

Free Iron content in High dose IV Iron products



Labile Iron Pools in Parenteral Iron Products



Blue bars indicate results obtained without pH adjustment.
Red bars indicate results obtained following adjustment to pH 7.0

Jahn MR, et al. *Eur J Pharm Biopharm*. 2011;78:480-491.

Tryptase Levels After Minor Infusion Reactions

- N=>200 since 2002

- Mean change from baseline 0.0 mg/dl
- Recent publication in Allergy and Immunology[1] reported 36% of patients with diagnosis of “anaphylaxis” had normal tryptase levels
- Earliest levels drawn at one hour
- Concluded that better marker is necessary
- No published data extant describing criteria for diagnosing anaphylaxis in recipients of IV iron
- No publication extant supports anything other than iron infusion reactions when HMW ID is excluded[2] except for
- One published “anaphylactic reaction” with elevated tryptase[3]

(2) Novey et al, Ann Allergy,1994;72:224-228, (1) Sala-Cunill et al 2013; Allergy and Immunology, (3) Santosh et al 2011; NDT

Baseline Mast Cell Tryptase Elevated in Hemodialysis Patients

- Serum mast cell tryptase levels were above 11.4 µg/l (95th percentile) in **84 of 93**
- The intensity of pruritus correlated significantly (p = 0.014) with the tryptase levels, an association not yet shown for other mast cell-related parameters[1].
- The minimal increase in acute total tryptase levels considered clinically significant was suggested to be 2 + 1.2 X baseline tryptase levels[2].

1. Journal der Deutschen Dermatologischen Gesellschaft, 3:343–3472. 2. Valent P et al Int Arch Allergy Immunol. 2012;157:215-25.

Role of Dextran Antibodies

- The presence of dextran antibodies prior to ID infusion was not associated with ADRs
- No increase in antibodies after 9 month course of ID
- ADRs were not IgE mediated
- Most normal people have circulating antibodies to dextran
- Dextran antibodies considered clinically insignificant

Richter et al 1982; Immunology today 3:132-138

IDA-301- Adverse Events

AE Category	Ferumoxytol N=608		Placebo N=200		Total N=808	
	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)
All AEs	718	299 (49.2)	206	86 (43.0)	924	385 (47.6)
Related* AEs	176	89 (14.6)	25	15 (7.5)	201	104 (12.9)
SAEs	23	16 (2.6)	6	6 (3.0)	29	22 (2.7)
Related* SAEs	4	4 (0.7)	0	0	4	4 (0.5)
AEs of Special Interest- protocol-defined[1]	26	22 (3.6)	2	2 (1.0)	28	24 (3.0)
Cardiovascular AE Composite Endpoint[2]	6	5 (0.8)	0	0	6	5 (0.6)
AEs Resulting in Temporary Discontinuation of Study Drug	4	3 (0.5)	0	0	4	3 (0.4)
AEs Resulting in Permanent Discontinuation of Study Drug	17	12 (2.0)	2	1 (0.5)	19	13 (1.6)
AEs Resulting in Study Discontinuation	5	3 (0.5)	3	2 (1.0)	8	5 (0.6)
Death[3]	2	2(0.3)	1	1 (0.5)	3	3 (0.4)

[1] AEs of Special Interest include hypotension and hypersensitivity as defined in the protocol

[2] Cardiovascular AE Composite Endpoint includes myocardial infarction, heart failure, moderate to severe hypertension and hospitalization due to any cardiovascular cause.

[3] Reported as unrelated to study drug by the investigator.

* Related AEs are those with relationship classified by investigator as related to study drug. Vadhan-Raj AJH 2013

Primary Endpoint: Safety
Summary of Adverse Events

	Ferumoxytol N=80			Iron Sucrose N=82		
AE Category	**Events**	**Subjects N (%)**	**Events per subject**	**Events**	**Subjects N (%)**	**Events per subject**
All AEs	86	38 (48)	2.3	161	53 (65)	3.0
Related AEs	8	8 (10)	1.0	46	13 (16)	3.5
SAEs	8	7 (9)	1.1	11	6 (7)	1.8
Related SAEs	1	1 (1)	1.0	1	1 (1)	1.0
AEs of Special Interest[1]	1	1 (1)	1.0	4	2 (2)	2.0
AEs leading to drug discontinuation	1	1 (1)	1	7	4 (5)	1.3

[1] Includes acute AEs of moderate-to-severe hypotension and hypersensitivity reactions

Macdougall et al, cJASN 2014

Personal Communication to both authors

- In Vadhan-Raj's study an attempt to administer the ferumoxytol over 17 seconds was standard
- In FIRST administration occurred over a minimum of 60 seconds

Current Epocrates Section on IV iron therapy

Comments

- If patients cannot tolerate oral iron or have such a rapid iron loss that oral iron cannot keep up with the losses, iron can be given parenterally.(B) Evidence In addition, intravenous iron has shown superior efficacy to oral iron in the treatment of iron deficiency anemia related to malignancy and inflammatory bowel disease.[63] [64] [65]
- About 1% of patients may have an anaphylactic reaction to iron dextran and so a test dose is mandatory.

Adverse Events

n=396	Patients n (%)
Any AE	22 (5.6)
Any Serious AE	0 (0)
AEs resulting in discontinuation	1 (0.3)
AEs requiring intervention	9 (2.3)
Decreased infusion rate or temporary interruption alone	2 (0.5)
IV methylprednisolone alone	1 (0.3)
Acetaminophen	2 (0.5)
Temporary infusion interruption plus IV methylprednisolone	4 (1.0)
AEs occurring in >1 patient	
Back pain	7 (1.8)
Headache	4 (1.0)
Myalgia	3 (0.8)
Nausea	3 (0.8)
Chest discomfort	2 (0.5)
Flushing	2 (0.5)
Nasal congestion	2 (0.5)
Pruritus	2 (0.5)

Auerbach M, et al. *Am J Hematol*. 2011;86:860-862.

Conclusion

- IV iron is safe and effective across a broad spectrum of anemias and much safer than most physicians realize
- The perception of serious danger is folklore fueled by inappropriate premedication and interventions for self-limited minor infusion reactions and publications using proscribed comparison methodologies
- Is it possible that reported SAEs with IV iron, when HMW ID is avoided are overwhelmingly iatrogenic?