CAN IRON DEXTRAN BE GIVEN WITHOUT A TEST DOSE?

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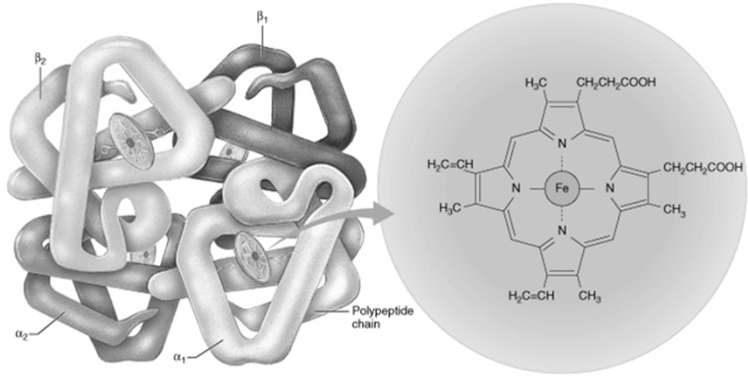


DISCLOSURE

- I do not have any financial interests or commercial interests in the products discussed during this educational activity.

OBJECTIVES

- Review the prevalence of infusion reactions with iron dextran
- Evaluate European guideline recommendations for iron dextran administration
- Discuss strategies for omitting the iron dextran test dose

IRON FORMULATIONS

	Iron dextran (INFeD®)	Iron sucrose (Venofer®)	Ferrous ferumoxytol (Feraheme®)	Ferrous gluconate (Ferrlecit®)	Ferric carboxymaltose (Injectafer®)
Indication	IDA	IDA with CKD	IDA with CKD	IDA in patients on HD and epoetin	IDA
Dose	1000 mg	200-400 mg	510 mg	125 mg	<50 kg: 15 mg/kg ≥50 kg: 750 mg
Average # of doses	1 dose	5 doses	2 doses	8 doses	2 doses separated by 7 days
Administration time	~3 hours	≤200 mg: 15 minutes 300 mg: 1.5 hours 400 mg: 2.5 hours	15 minutes	1 hour	15 minutes
AWP Cost	$606.20 per 1000 mg dose	$600.00 per 200 mg dose $3000.00 per 1 g dose	$876.00 per 510 mg dose	$381.60 per 125 mg dose $3052.80 per 1 g dose	$1169.69 per 750 mg dose

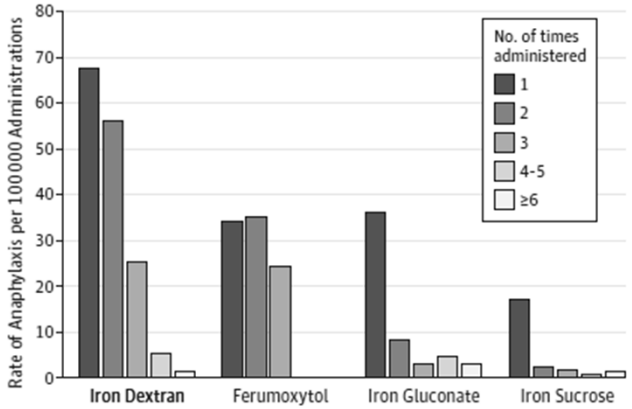
AWP: average wholesale price
CKD: chronic kidney disease
HD: hemodialysis
IDA: iron-deficiency anemia

Lexi-Comp Online. Accessed March 24, 2017.

HYPERSENSITIVITY PREVALENCE

- Low molecular weight iron dextran (LMW ID) 165,000 Da
- High molecular weight iron dextran (HMW ID) 265,000 Da
- Reported adverse event rate with HMW ID is 28%
- Wang, et al. reports that the incidence of anaphylaxis with iron dextran is 0.61%
  - Study did not differentiate incidence between high and low molecular weight iron

Figure 2. Rate of Anaphylaxis by IV Iron Products and Number of Administrations



No. of times administered	No. of users	No. of users	No. of users	No. of users
1	247 500	82 117	94 400	264 166
2	126 678	48 359	72 464	196 201
3	90 874	12 244	64 834	169 788
4-5	129 799	13 173	105 438	251 284
≥6	495 851	8778	312 971	550 444

IV indicates intravenous.

Kidney Int. 2002;61(5):1830-1839

HYPERSENSITIVITY PREVALENCE

- In 1997, due to a shortage of LMW ID, substitution with HMW ID resulted in a 1100% increase in adverse drug events (ADEs) reported to the Food & Drug Administration (FDA)

- Waziri, et al. reported no difference in adverse events or anaphylactic reactions between iron sucrose and LMW ID

Adverse events	Iron sucrose N = 34	LMWID N = 33	P-value
≥1 event	5 (14.7%)	9 (27.3%)	0.21
Hypotension	1 (2.9%)	4 (12.1%)	0.19
Dizziness	1 (2.9%)	2 (6.1%)	0.61
Elevated blood pressure	1 (2.9%)	1 (3.0%)	0.98
Chest tightness	0 (0.0%)	2 (6.1%)	0.24
Joint pain	1 (2.9%)	2 (6.5%)	0.61
Urticaria	0 (0.0%)	1 (3.0%)	0.49
Vomiting	1 (2.9%)	0 (0.0%)	0.98
Diarrhoea	0 (0.0%)	1 (3.0%)	0.49
Tachycardia	0 (0.0)	1 (3.0%)	0.49
Pain at injection site	1 (2.9%)	0 (0.0%)	0.98

J Am Soc Nephrol. 2008;19(5):833-4
Clin Kidney J. 2016;9(6):817–822

CURRENT PRACTICE IN THE UNITED STATES

- HMW ID no longer commercially available

- Before initial treatment, a one time 25 mg test dose IV is indicated per package insert
  - Non-anaphylactic reactions usually occur within minutes
  - Monitor for anaphylactic-type reactions for at least 1 hour prior to administration of the therapeutic dose

- Therapeutic dose usually infused over 3 hours

- No recommendations on when or how often to repeat test dose

Iron dextran (INFeD) injection [package insert]
http://www.suprememed.com/media

TEST DOSE PITFALLS

- Both non-anaphylactic and anaphylactic reactions may still occur despite a patient not experiencing a reaction to the initial test dose

- Lack of understanding and false sense of security may decrease monitoring
  - Greater concern that early signs of impending anaphylaxis may be missed
    - Rash
    - Runny nose
    - "Strange feeling"

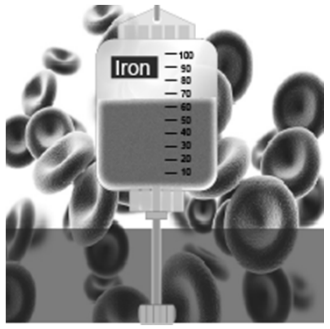
Nephrol Dial Transplant. 2005;20(7):1438-42.

EUROPEAN GUIDELINES

- All patients are informed of the risk and seriousness of a hypersensitivity reaction
- Iron dextran (CosmoFer®) test dose omitted
- Only nursing staff trained in recognizing and managing anaphylactic reactions are to administer any iron formulation
- Patients are monitored for hypersensitivity reactions for at least 30 minutes following the infusion

Blood Transfus. 2014;12(3):287–289.

INFUSION RECOMMENDATION



- Rampton, et al.
  - Test dose omitted

Standard risk patients

• Initiated iron dextran at 50% the normal infusion rate
  • Increased to normal infusion rate after 15 minutes if patient did not display any symptoms of hypersensitivity
  • Monitored patient every 15 minutes during infusion and for 30 minutes after the infusion completes

For high risk patients, initiated at 10% the normal infusion rate
• Previous reaction to iron • History of other drug allergies • Mastocytosis • Severe respiratory or cardiac disease • Old age • Treatment with beta-blockers or ACE inhibitors • Pregnancy • Systemic inflammatory disease • Anxiety

Haematologica. 2014; 99(11): 1671–1676.

SUPPORTING LITERATURE

- Aurbach, et al.
  - Test dose administered to all iron dextran naïve patients
    - Total of 396 patients and 570 iron dextran infusions evaluated
  - 15 minute observation period
  - Premedication with 125 mg IV methylprednisolone only administered to patients with multiple drug allergies, asthma, inflammatory bowel disease, and/or previous iron dextran reactions
  - Remainder of 1000 mg (20 mL) dose in 250 mL normal saline administered at 300 mL/hr
  - If an adverse reaction occurred
    - Infusion held
    - Patient monitored for 1 hour
    - Patient evaluated to determine clinical stability
    - Infusion restarted at 100 mL/hr

- No anaphylactic reactions and no serious adverse effects were reported

Am J Hematol. 2011;86(10):860-2.

OREGON HEALTH & SCIENCE UNIVERSITY PRACTICES

- Previous
  - A test dose was indicated for all new iron dextran administrations
  - Repeat test dose was indicated if a patient had not received iron dextran in the last 6 months
  - Remaining therapeutic iron dextran dose was administered over 3 hours
  - As needed hypersensitivity medications were ordered in the infusion plan

- Current
  - A test dose is indicated for all new iron dextran administrations
  - No subsequent test doses are indicated
  - Iron dextran is administered over 3 hours
  - As needed hypersensitivity medications are ordered in the infusion plan

CONCLUSION

- The incidence of anaphylactic reactions with LMW ID is comparable to iron sucrose
- An uneventful test dose does not ensure that the patient will not react to the therapeutic dose
- European guidelines have abandoned the need for an iron dextran test dose in treatment naïve patients
- In the United States, repeat test doses may not be required for subsequent iron dextran administration; however, there is increased emphasis on monitoring

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