Drugs and Therapeutic Backgrounder:

Parenteral iron safety

Overall rates of severe adverse events with parenteral iron are low. Hypersensitivity reactions to parenteral iron, with currently available formulations, are extremely rare. Infusion reactions are less rare, transient, do not require treatment with epinephrine, and usually do not prevent resuming the infusion or future doses.

Background

A recent meta-analysis including over 10,000 patients found overall there is no increase in severe adverse events (SAEs) with parenteral iron preparations compared to controls (oral iron and placebo)[1]. There was no increased risk of serious infection with parenteral iron but there is increased risk of serious infusion reactions, particularly with sodium ferric gluconate[1]. Overall there was no increased mortality associated with parenteral iron, and no increased risk of adverse events that required discontinuation[1].

The risk of acute SAE and death with parenteral iron is very low compared to blood transfusions (1:200,000 compared to 1:21,413)[3]. It is estimated that there has been approximately 1 death per 5 million doses for parenteral iron when older, more reactive, high molecular weight iron dextran was available[2]. Currently available newer parenteral iron formulations have fewer adverse effects and anaphylaxis rates than older higher molecular-weight dextran formulations[1].

Risk Factors

Factors that may increase the risk for development or severity of hypersensitivity* reactions to parenteral iron include[2, 3]:

*hypersensitivity includes anaphylaxis, infusion reactions, and acute isolated adverse effects

- Previous reaction to parenteral iron
- History of other drug allergies
- Mastocytosis
- Fast infusion rate
- Male sex
- Vigorous physical exercise
- Severe asthma or eczema
- Severe respiratory or cardiac disease
- Old age
- Treatment with beta-blockers or ACE inhibitors
- Pregnancy (first trimester)★
- Anxiety (patient or staff)

Due to potential hypersensitivity reactions, administration in a facility with equipment and personnel for resuscitation is recommended by manufacturers and in guidelines[3]. Vital signs should be monitored at baseline and closely for the first few minutes of the infusion and then regularly throughout infusion and for 30 minutes afterward[5].

Mechanisms

Two main mechanisms for hypersensitivity reactions are IgE mediated and complement-activation related pseudo-allergy and the two are not clinically distinguishable[6]. Hypersensitivity reaction symptoms include: facial swelling, tachycardia, hypotension, angioedema, stridor, cough, wheeze, difficulty breathing, vomiting, diarrhea, dermal manifestations (blistering, epidermal detachment, pustules, purpura, necrotic lesions, maculopapular rash, etc.). Anaphylaxis is a severe, life-threatening hypersensitivity reaction which is a clinical diagnosis (not based on mechanism)[5, 3]. A third type of reaction, termed the Fishbane reaction, is a mild acute reaction to parenteral iron characterized by transient flushing, chest and back tightness, and joint pain. Symptoms in this reaction disappear spontaneously, do not usually recur with re-challenge, and are thought to be due to labile iron rather than IgE or complement-mediated.

★ Contraindicated in first trimester; iron isomaltoside contraindicated in pregnancy

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Guidance

Test doses are not recommended since there is a risk of hypersensitivity reactions with every dose even if previous doses were well tolerated[3, 4]. To reduce the occurrence of reactions, it is suggested to begin the initial iron infusion at 50% of the recommended rate until it is clear the infusion is being well tolerated (for 10-15 minutes) or 10% of the recommended rate if the above risk factors are present[2, 3]. Lower initial doses are also recommended in patients with risk factors[3]. If the patient experiences a severe/life-threatening hypersensitivity reaction to any parenteral iron, other formulations should not be given[2]. If a mild to moderate reaction is experienced, another formulation may be tried with caution[2]. Strategies to minimize reaction with re-challenge include: 1) slowed infusion rate, 2) lower dose, 3) switching formulation, 4) pre-medication with corticosteroids, antihistamine and acetaminophen (unknown benefit)[3]. Patients should be educated on the difference between reaction types to reduce anxiety which can exacerbate symptoms.

Canadian consensus statement on management of hypersensitivity reactions classify reactions in to 4 types[3]:

Reaction Type	Symptoms	Recommended Intervention
Anaphylaxis	Acute life-threatening systemic reaction involving 2+ organ systems: Respiratory **and** 1 of: skin; cardiovascular; GI **or** hypotension **or** angioedema of tongue/airway alone	Stop infusion • 0.3-0.5 mL epinephrine 1:1000 IM • Lie patient horizontal • Supportive care if required • Corticosteroids can be given (effectiveness unknown)
Isolated symptoms	Isolated symptoms of hypersensitivity: • IV site irritation • Urticaria • Nausea • Diarrhea • Abdominal pain	Stop infusion • Observe and monitor for further signs of hypersensitivity • Consider second generation H1 antagonist if urticaria (consider H2 if IV route only available) • If symptoms resolve, consider restarting infusion at slowed rate
Fishbane reaction (or “free iron reactions”)	Acute non-life threatening transient symptoms: • Facial flushing • Truncal myalgia • Chest tightness • Joint pains • No symptoms of anaphylaxis ★	• Stop infusion, observe and monitor patient • Symptoms will usually resolve and not recur with re-challenge • When symptoms resolve, restart infusion at reduced rate • Treating as anaphylaxis can exacerbate symptoms
Delayed reactions	Delayed anaphylaxis occurring more than 30 min after end of infusion is rare • Fever • Myalgia/arthralgia • Headache	• Advise patient to monitor for first 24 hours • Treat with acetaminophen (avoid NSAIDs)

Document all hypersensitivity reactions. Serious reactions may require additional reporting to Health Canada, as per Vanessa’s Law. Recommended medications to have readily available: epinephrine (1:1000 IM), inhaled beta agonist nebules, glucocorticoid (e.g. hydrocortisone 200 mg or methylprednisolone 50-100 mg), IV H1 antagonist (e.g. diphenhydramine), IV H2 antagonist (e.g. ranitidine)[3].

★ Specifically no hypotension, mucosal involvement, other organ systems e.g. respiratory or GI

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References

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5. AHS Parenteral Drug Manual. Available online at: http://webappsint.albertahealthservices.ca/pharmacy/pm/pm_index.asp.
6. Lim, W. Iron Metabolism and management of iron deficiency. Hematology Rounds presentation, May 2019.

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