Clinical Pharmacology & Toxicology Pearl of the Week

~ Not All That Wheezes Is Anaphylaxis: Navigating Pseudo-Allergic Reactions to IV Iron in CKD ~

Case presentation:

The patient is a 48-year-old female with a background medical profile including Chronic Kidney Disease G5A3 (Cr 495, GFR 8) secondary to biopsy proven IgA nephropathy awaiting peritoneal dialysis start, anemia, gout, hypertension, and menorrhagia. Anemia profile demonstrates low serum iron and iron saturation index (Hb 80, Iron 5, Iron saturation index 0.08, TIBC 66) that has transiently improved while being on daily oral iron and weekly Aranesp therapy (Hb 92, MCV 84, Iron Saturation Index 0.10, Iron 7, TIBC 68).

On receiving Monoferric IV iron (1000 mg ferric derisomaltose), she developed chest and throat tightness associated with emesis within minutes of receiving ~1-3 ml. The iron infusion was stopped and patient was given a single dose of methylprednisolone following which all symptoms resolved.

Questions for Clinical Pharmacology:

1. Is there cross-reactivity between different IV iron formulations?
2. Is there a pretreatment regimen that could be considered if IV iron is absolutely necessary?
3. What alternative options are available if patient cannot use IV iron?

Case Discussion:

- Studies have shown that rates of mild reactions are approximately 1:200 and rates of major reactions are approximately 1:200,000. Large studies have shown that all IV iron formulations are associated with adverse effects, so from a safety standpoint no one product is preferred.

- Being truly allergic to IV iron is very rare—almost all reactions are complement activation–related pseudo-allergy, which are idiosyncratic infusion reactions that can mimic allergic reactions.

- Key symptoms, including rapid onset (within minutes), itching, throat and chest tightness, vomiting, resolution after steroid administration, and no prior exposure are consistent with a complement activation-related pseudo-allergy (CARPA) rather than an IgE-mediated anaphylactic reaction.

- For mild reactions, simply stopping the infusion and restarting 15 minutes later at a slower rate will suffice. For more severe reactions, corticosteroids may be of benefit. Diphenhydramine should be avoided because its side effects of mouth dryness, tachycardia, diaphoresis, somnolence, and hypotension can be mistaken for worsening of the reaction.

- There is no convincing evidence of cross reactivity between different IV formulations. One study from a JAMA article in 2022 found significant differences in the rate of infusion reactions among IV iron formulations, with the highest rates of reaction occurring among those who received iron sucrose (4.3%) and lowest among those who received ferric carboxymaltose (1.4%).

- Monoferric (ferric derisomaltose) has low rates of hypersensitivity, but reactions can still occur. Cross-reactivity between different iron formulations is not guaranteed however other formulations of intravenous iron may be better tolerated.

- Premedication (e.g., corticosteroids, antihistamines) is not routinely recommended because it may mask early signs of a reaction or even worsen symptoms (e.g., diphenhydramine may cause flushing and hypotension secondary to orthostatic hypotension from alpha adrenergic blockade). However, studies suggest that routine use of premedication be limited only to those with substantial risk factors (such as previous reaction to IV iron, if a fast infusion rate is used, multiple drug allergies, severe asthma, or atopy)

- In general, rechallenge to an alternate IV iron formulation is safe. A graded challenge or test dose with a different formulation (e.g., iron sucrose) or re-challenge with IV ferric derisomaltose (Monoferric) might be considered under close monitoring.

Recommendations:

Alternative IV Iron formulations:

1. Consider using other IV iron formulations which have lower rates of severe reactions. Options include the following:

    - Iron sucrose containing 20 mg/ml elemental iron: This is used for people with CKD G1–G5 not receiving HD, but it requires multiple patient visits as 1000 mg cannot be given at a single sitting (5 doses of 200 mg over 5 weeks). Iron sucrose differs from other formulations in that the smaller carbohydrate core binds iron less tightly, resulting in significantly increased labile-free iron after administration and higher risk of hypersensitivity reaction. With the advent of

multiple low doses of iron sucrose, most studies have demonstrated similar safety profiles when compared with low molecular weight iron dextran.

- Ferric gluconate in sucrose complex (250 mg 4 doses weekly) containing 12.5 mg/ml elemental iron per dose.

- Low-molecular weight iron dextran containing 50 mg/ml elemental iron has lower hypersensitivity than high molecular weight dextran, however this requires at least 4-6 hours of infusion time.

- Ferumoxytol (Feraheme, AMAG Pharmaceuticals) is a superparamagnetic iron oxide coated with carbohydrate that also is approved as a magnetic resonance imaging contrast agent. Thus, the radiologist should be notified if magnetic resonance imaging is obtained within 3 months after infusion.

2. Oral Iron Supplementation: Feramax 300 mg/ day is the maximum dose.

3. Erythropoiesis-Stimulating Agents (ESAs): Once iron levels are adequately managed, ESAs can be used to stimulate red blood cell production.

4. Ferric Pyrophosphate Citrate: Administered via dialysate in patients undergoing dialysis, this can be an effective alternative to traditional IV iron.

References:

- KDIGO Anemia Guidelines (2024 draft update) https://kdigo.org/wp-content/uploads/2024/11/KDIGO-2025-Anemia-in-CKD-Guideline_Public-Review-Draft_Nov42024.pdf

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- Iron Formulations and Use in Adults. Van Doren L, Auerbach M. Hematology. American Society of Hematology. Education Program. 2023;2023(1):622-629. doi:10.1182/hematology.2023000495.

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