

Fatal anaphylactic reaction to iron sucrose in pregnancy: Iron-induced Kounis syndrome?

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Sir,

Parenteral iron preparations are administered to patients who are unable to tolerate or absorb oral iron preparations, or are unwilling to cooperate. Studies[[1](#)] have shown that iron absorption from food increases when the serum ferritin is below 30 ng/ml, and decreases when it is more than 300 ng/ml. In hemodialysis patients, in particular, oral absorption of iron does not occur when serum ferritin is approximately 50 ng/ml. Parenteral iron administration is occasionally associated with severe side effects. Intravenous iron preparations such as high and low molecular weight iron dextran, ferrous gluconate, and iron sucrose are associated with adverse effects at a rate of 38 per million.[[2](#)] Rapid iron infusion can cause adverse effects because it induces oversaturation of transferrin and releases free iron. Free iron is responsible for toxicity, hypersensitivity, and vasomotor reactions. The first adverse symptoms might be pruritus or burning sensation of the tongue, so an initial test dose of small amount of preparation followed by the whole dose is recommended. Intravenous iron generates oxidative stress, inflammation, endothelial dysfunction, as well as cardiovascular and renal injury. The propensity for these events is increased with non dextran iron. However, iron dextran, especially the large molecular form, is complicated by anaphylactic reactions and death. Iron sucrose is typically administered as a slow push injection or a 15-30 min infusion in doses of 100-200 mg. This requires multiple outpatient visits and repeated intravenous doses in order to achieve the standard therapeutic course of 1000 mg elemental iron. Iron dextran is given as a single dose, but this requires administration over a period of 4 to 6 h. In addition, iron dextran complexes can cause fatal dextran-induced anaphylactic reactions. Anaphylactic reactions to iron sucrose are rare and include generalized pruritus, burning sensation of the tongue, and peribuccal hyperaesthesia.

In the very interesting report published recently in this journal[[3](#)] a 20-year-old primigravida without any previous allergic history, suffering from severe iron deficiency anemia developed anaphylactic shock following an infusion of iron sucrose. Despite treatment with intravenous adrenaline, hydrocortisone, antihistamines, H₂ blockers, ventilatory and inotropic support, she succumbed from cardiac arrest within 24 h. Postmortem examination and pre and postmortem tryptase levels were not obtained.

This report raises some important clinical, therapeutic pathophysiological issues. The patient died from cardiac arrest within 24 h after she had taken the iron sucrose infusion and despite vigorous antianaphylactic therapy. Was the cause of death a fatal Kounis syndrome?[[4](#)] She received, wisely, adrenaline, hydrocortisone, antihistamines, H₂ blockers, ventilatory and inotropic support. Had this combined treatment served as an adjunct to iron sensitivity? Is the coronary artery injury a primary effect of anaphylaxis leading to cardiac arrest and Kounis syndrome?

Today, Kounis syndrome is defined as the concurrence of acute coronary syndromes such as coronary spasm and coronary thrombosis with conditions associated with mast cell and platelet activation. It is

caused by inflammatory mediators released during the mast cell degranulation process and/or platelet activation via FcγRI, FcγRII, FcεRII, and FcεRII receptors situated on the platelet surface.[4] Assumed that the patient's symptoms such as giddiness and difficulty in breathing that appeared soon after on sucrose infusion were due to an allergic reaction to iron, a Kounis syndrome type I leading to cardiac arrest could not be excluded. Ideally pre and postmortem tryptase measurements would have corroborated this diagnosis. The combination of treatment applied to this patient was appropriate but some of the given medications may have acted as antigens. It is known that patients simultaneously exposed to several drugs acting as antigens have more symptoms than mono-sensitized individuals. Furthermore, IgE antibodies with different specificities can have an additive effect and even small amounts of corresponding allergens are able to trigger mediator release when the patient is simultaneously exposed to them. Surprisingly, corticosteroids,[5] H2 blockers,[6] antihistamines,[7] and adrenaline, may themselves act as antigens. For example, adrenaline contains, as preservative, sodium metabisulfite that can induce hypersensitivity, anaphylaxis, and even death from Kounis syndrome. Anaphylactoid shock has been reported during epidural anesthesia for cesarean section, in which the responsible agent was metabisulfite, an additive agent of adrenaline-containing local anesthetic.[8] Therefore, a therapeutic dilemma should appear in the sulfite-sensitized patient that only few physicians are aware of.

There is experimental and clinical evidence that the primary target of the released anaphylactic mediators is the coronary vasculature resulting in damage of the corresponding myocardial tissue. This can lead to cardiac arrest as in the described patient. Experiments with ovalbumin-sensitized guinea pigs have shown that the registered anaphylactic damage is not due to arterial hypotension and this should be definitely excluded.[9] Furthermore, patients with anaphylactic cardiac shock who do not respond to intravenous fluid expansion and antiallergic therapy, respond successfully only to acute coronary event treatment protocol.

Anaphylactic shock seems to be treacherous situation that needs meticulous analysis, detailed patient assessment and specialized treatment.[10] Physicians dealing with the treatment of anaphylactic shock should be aware of all aforementioned cautions and precautions in order to achieve favorable therapeutic outcomes.

References

1. Eschbach JW, Cook JD, Scribner BH, Finch CA. Iron balance in hemodialysis patients. *Ann Intern Med.* 1977;87:710–3. [PubMed: 931207]
2. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmén J. Update on adverse drug events associated with parenteral iron. *Nephrol Dial Transplant.* 2006;21:378–82. [PubMed: 16286429]
3. Mishra A, Dave N, Viradiya K. Fatal anaphylactic reaction to iron sucrose in pregnancy. *Indian J Pharmacol.* 2013;45:93–4. [PMCID: PMC3608307] [PubMed: 23543624]
4. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): A natural paradigm? *Int J Cardiol.* 2006;110:7–14. [PubMed: 16249041]
5. Sherman S, Oleinikov K, Mouallem M. [Allergic reaction induced by steroid therapy.] [Article in Hebrew] *Harefuah.* 2013;152:21–2. 59,60. [PubMed: 23461021]
6. Cho HJ, Yoo HS, Park SY, Yang EM, Yoon MG, Park HS, et al. A case of cimetidine-induced immediate hypersensitivity. *J Investig Allergol Clin Immunol.* 2012;22:216–8.
7. Mur Gimeno P, Alfaya Arias T, Iglesias Aranzazu M, Lombardero Vega M, Sastre B. Anaphylactic shock caused by antihistamines. *J Investig Allergol Clin Immunol.* 2011;21:321–2.
8. Soulat JM, Bouju P, Oxeda C, Amiot JF. [Anaphylactoid shock due to metabisulfites during cesarean section under peridural anesthesia.] [Article in French] *Cah Anesthesiol.* 1991;39:257–9. [PubMed: 1933525]
9. Felix SB, Baumann G, Berdel WE. Systemic anaphylaxis — Separation of cardiac reactions from

respiratory and peripheral vascular events. *Res Exp Med (Berl)* 1990;190:239–52. [PubMed: 2218074]

10. Cevik C, Nugent K, Shome GP, Kounis NG. Treatment of Kounissyndrome. *Int J Cardiol.* 2010;143:223–6. [PubMed: 20206392]

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