Anaphylaxis to medications containing meat byproducts in an alpha-gal sensitized individual

Christine Muglia, MD[a], Indrani Kar, PharmD[b,c], Min Gong, PharmD[b,c], Evelyn R. Hermes-DeSantis, PharmD, BCPS[b,c], and Catherine Monteleone, MD[d]

Clinical Implications

- We present a case of alpha-gal allergy in conjunction with allergic reactions to medications that contain magnesium stearate, which may be of bovine origin. Physicians should be aware of the possible cross-reactivity between alpha-gal and medications that contain meat byproducts because inadequate avoidance can result in anaphylaxis.

TO THE EDITOR:

Delayed anaphylaxis to red meat is an allergy that has been increasingly recognized over the last few years. The mechanism involves an IgE reaction to an oligosaccharide, galactose-alpha-1,3-galactose (alpha-gal), found in nonprimate mammals and tick glycoproteins.[1] The reaction can consist of anaphylaxis, urticaria, or angioedema and occurs in response to ingestion of mammalian meat, such as beef, lamb, pork, or venison.[1] The mechanism of sensitization has been found to be associated with bites from *Amblyomma americanum*, the lone star tick.[2] The proposed mechanism of sensitization is that the tick bite stimulates production of IgE to alpha-gal, and the IgE then binds to high-affinity IgE receptors on mast cells and basophils. When mammalian meat is later ingested by a sensitized individual, the alpha-gal antigen in the meat binds the IgE, which results in the release of mediators, such as histamine, from these cells.[3]

Magnesium stearate is a pharmaceutical excipient, which is added to tablets to facilitate lubrication during powder particle molding in the manufacturing process. This inactive ingredient can be synthesized from organic fatty acids of either bovine or vegetable origin. It is produced by a chemical reaction of magnesium chloride with sodium stearate or by a reaction of magnesium oxide, hydroxide, or carbonate with stearic acid at elevated temperatures. Stearic acid has a chain length with a beneficial friction coefficient reduction, which allows multilayers to form on the surface of medication and facilitates lubrication.[4]

Although it is a theoretical concern, there have not yet been any reports of a cross-reaction between allergy to alpha-gal and medications that contain magnesium stearate, a meat byproduct. Our case presents a patient with alpha-gal allergy as well as allergic reactions to numerous medications that contain magnesium stearate. The correlation between his reactions to meat and to these medications suggests that the medication reactions may have been due to alpha-gal in the magnesium stearate. Alpha-gal has not been definitively found in magnesium stearate, as this study has yet to be conducted. The correlation is theoretical.

Our patient is a 48-year-old man with hypertension, Keinboch's disease with chronic pain, and recurrent anaphylaxis who presented for evaluation of allergy to red meat. He had no personal or family history of asthma, allergic rhinitis, or other food allergy. He reported that for the last 25 years, he has had episodes of edema of the larynx and tongue, diffuse hives, dyspnea, wheezing, abdominal cramping, diarrhea, edematous testicles, and a sense of impending doom approximately 4 to 5 hours after eating hamburger, steak, or venison. Reactions typically required treatment with epinephrine. The delay in time between eating dinner and the reaction caused a delay in diagnosis for many years. Notably, he had been a hunter since the age of 11 and had sustained countless tick bites over the years.

He was evaluated by an allergist and had an alpha-gal IgE of 95.90 (Labcorp: normal <0.35) and a tryptase level of 9 ng/mL (Quest: normal 2-10). He also had a venison IgE of 0.35, pork and lamb IgE of 0.14, but beef, chicken, and turkey IgE of <0.08. It is important to note that his negative beef immunoassay in the setting of a positive immunoassay to alpha-gal is not consistent with the literature on alpha-gal.[5] However in our evaluation, and similar to what has been described in related reports, he was originally negative to milk and meats on commercially available percutaneous skin testing, but subsequent prick-prick skin testing with fresh meats revealed positive responses to beef, lamb, and pork.[6,7]

With avoidance of red meats, he has experienced no reactions; however, he has had symptoms with medications that contain magnesium stearate. After taking medications prescribed as a gelatin capsule, including acetaminophen (Tylenol, McNeil Consumer Healthcare, Fort Washington, Pa) and naproxen (Aleve, Bayer HealthCare LLC, Whippany, NJ), he experienced immediate onset diarrhea and chest tightness, which resolved with the use of diphenhydramine (Benadryl, McNeil Consumer Healthcare, Fort Washington, Pa). With lisinopril tablets (Aurobindo Pharma Limited, Hyderbad, India), he experienced laryngeal edema, abdominal cramping, nausea, and diarrhea, which resolved after stopping lisinopril. Approximately 3 to 4 hours after taking hydrocodone bitartrate and/or acetaminophen (Vicodin, AbbVie Inc, North Chicago, Ill), he experienced hives, which were relieved 4 hours after the use of diphenhydramine (Benadryl). Similarly, he experienced hives after the use of clonidine.

Each of these medications has one inactive ingredient in common: magnesium stearate, a potential meat byproduct. According to the manufacturers, magnesium stearate in the patient's medications was derived from either bovine or vegetable sources. The possibility that alpha-gal may be present in the patient's medications warrants consideration. Ever since he identified magnesium stearate as the common denominator, he has avoided medications that contain magnesium stearate and has had no further reactions. He currently tolerates compounded oral suspensions of clonidine and oxycodone.

Our case highlights the possible cross-reaction between allergy to alpha-gal and meat byproducts, such as magnesium stearate, which has yet to be described in the literature. Because patients with alpha-gal allergy can experience life-threatening anaphylaxis to mammalian meat, it is exceedingly important to recognize the

cross-reactivity of meat byproducts used in common medications. To provide complete information to our patients regarding substance avoidance, we must first identify products that are cross-reactive with alpha-gal.

Our patient's reactions to gelatin capsules do not allow us to isolate magnesium stearate as the cross-reactive allergen, because gelatin is also a meat byproduct. His reaction to lisinopril tablets that contain magnesium stearate, but not gelatin, makes the case stronger for cross-reaction between alpha-gal and magnesium stearate, but still does not confirm it. Although lisinopril can cause bradykinin-induced angioedema, intestinal angioedema, as described in our patient, is rarely associated with lisinopril. His reaction to hydrocodone bitartrate and/or acetaminophen (Vicodin) suggests magnesium stearate as the cross-reactant because it contains magnesium stearate, but not gelatin. However, hydrocodone, as an opiate, could also cause direct mast cell degranulation.

Pharmaceutical manufacturers do not currently test products for alpha-gal content. Additionally, they are not required by the Food and Drug Administration to report changes in inactive ingredients on the package insert. If a medication contains any type of meat byproduct, such as magnesium stearate and gelatin, the medication may potentially contain the alpha-gal epitope. Gelatin, specifically derived from beef, has been shown to have alpha-gal cross-reactivity.[8] Currently, no comprehensive list of medications that contain meat byproducts is available. To obtain meat byproduct information, manufacturers must be contacted, which may delay patient care.[9] Practitioners need to be cautious when reviewing medication therapy in patients with alpha-gal allergy, so as to avoid unnecessary exposure to alpha-gal through medications.

Multiple patients with alpha-gal allergy are making the connection between alpha-gal allergy and magnesium stearate themselves and are requesting further research on the topic via online blogs.[10] Further studies are needed to give scientifically sound answers to these patients' legitimate questions and concerns. Our case implicates magnesium stearate as a likely cross-reactant to alpha-gal allergy and would be a good starting point for future research.

[a]Department of Internal Medicine, Robert Wood Johnson Medical School, Rutgers, The State University of New Jersey, New Brunswick, NJ
[b]Department of Pharmacy Practice, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, New Brunswick, NJ
[c]Drug Information Service, Department of Pharmacy, Robert Wood Johnson University Hospital, New Brunswick, NJ
[d]Division of Allergy, Immunology, and Infectious Diseases, Robert Wood Johnson Medical School, Rutgers, The State University of New Jersey, New Brunswick, NJ

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Corresponding author: Christine Muglia, MD, Department of Internal Medicine, Robert Wood Johnson Medical School, Rutgers, The State University of New Jersey, 1 Robert Wood Johnson Place, MEB 358, New Brunswick, NJ, 08901. E-mail: mugliach@rwjms.rutgers.edu.

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