

A retrospective evaluation of heparin product reactions in patients with alpha-gal allergies

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ABSTRACT

Background: Alpha-gal allergy, also known as red meat allergy or alpha-gal syndrome, can present after bites of certain tick species that contain galactose-alpha-1,3-galactose (alpha-gal) carbohydrate. Following this exposure, patients may develop an allergic reaction after mammalian meat consumption. Some heparin products are derived from porcine intestinal tissue, and it is therefore possible that administering these medications to a patient with an alpha-gal allergy may trigger a reaction.

Objective: The purpose of this study was to evaluate the incidence of reactions to porcine heparin products in patients with an alpha-gal allergy.

Methods: A retrospective case series was conducted by review of electronic medical record data. Patients included were between the ages of 18 and 89 years, with a documented alpha-gal or red meat allergy and an admission to a hospital in the Sentara Healthcare system. The primary outcome was the incidence of allergic reactions upon exposure to heparin products in patients with a documented alpha-gal allergy.

Results: Patients with a documented alpha-gal allergy received a heparin product in 57 of 158 hospital visits (36.1%). Heparin products were tolerated in 56 of the 57 visits (98.3%). The incidence of an alpha-gal reaction to unfractionated heparin was 2.6% (1/39) while the incidence of an alpha-gal reaction to enoxaparin was 0% (0/22).

Conclusion and Relevance: Heparin products were associated with a low incidence of alpha-gal reactions among patients with documented alpha-gal allergy. It is possible that enoxaparin poses less of a risk for reaction in these patients compared to unfractionated heparin.

Introduction

An allergy to galactose-alpha-1,3-galactose (alpha-gal), also known as a red meat allergy or alpha-gal syndrome, is an allergy of growing concern in the southeastern United States. As an emerging disease, the exact incidence of the syndrome is not known. However, some studies have reported a prevalence of positive alpha-gal antibodies of approximately 18–22% in various populations in a few southeastern states. (Commings et al., May) The rising prevalence of this allergy can be attributed to the increasing population of the Lone Star tick in this geographic region. (Platts-Mills et al., 2015; Allergy, 2019) The carbohydrate galactose-alpha-1,3-galactose, commonly referred to as alpha-gal, is transmitted through tick bites and can cause an immune response through development of immunoglobulin IgE in humans. The same carbohydrate is found on the surface of proteins in several

non-primate mammals including cows, pigs, lambs and goats. It is not found in humans. (Steinke et al., 2015) The Centers for Disease Control and Prevention (CDC) state that an alpha-gal allergy may be potentially life-threatening, as symptoms can range in severity from rash or hives to anaphylaxis. (Allergy, 2019)

This priming of the immune system to alpha-gal confers a reaction to red meat, however the extent of the risk with various medications or medical devices derived from mammals is unknown. Recent evidence has suggested that animal-derived medical devices such as catgut sutures, animal heart valves, and topical hemostatic agents, as well as medications of mammalian origin, may all be the cause of an IgE-mediated immune response in those with an alpha-gal allergy. (Holbert et al., 2020; Slayden et al., May-Jun; Akella et al., 2017; Stone et al., Jan) Anaphylaxis upon exposure to intravenous cetuximab, which is known to contain alpha-gal, is well-documented in patients with

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alpha-gal allergies. (Chinuki and Morita, 2019) Other reports have described reactions to vaccines, levothyroxine, liothyronine, or gelatin- or magnesium stearate-containing pharmaceuticals among patients with alpha-gal allergy. (Slayden et al., May-Jun; Akella et al., 2017; Stone et al., Jan) It is possible that any medication that may contain animal byproducts may trigger an IgE-mediated reaction to alpha-gal in this population.

Heparin products are frequently used for the treatment and prevention of thrombotic conditions, such as deep vein thrombosis and thromboembolism in atrial fibrillation. However, some heparin products, including unfractionated heparin (UFH) and low molecular weight heparins (LMWHs) such as enoxaparin, are derived from porcine intestinal tissue, and it is therefore possible that administering these medications to a patient with an alpha-gal allergy may trigger a reaction. The current data evaluating heparin products in patients with alpha-gal allergies is limited to case reports, small case series, and a cohort study with high-dose UFH. (Hawkins et al., 2020; Mawhirt and Banta, 2019; Crow et al., 2019; Mozzicato et al., 2014; Kleiman et al., 2017) With the increasing prevalence of this allergy in the United States and the lack of data surrounding animal byproducts that may invoke an allergic response, further study is warranted.

The purpose of this study was to evaluate the incidence of allergic reactions to UFH and enoxaparin in patients with alpha-gal allergy.

Methods

We conducted a retrospective case-series study using electronic medical record (EMR) data to identify patients with an alpha-gal allergy who received either UFH or enoxaparin from January 1, 2018 to July 20, 2020. Patient visits were identified using an allergy report from the EMR which was then manually evaluated for inclusion and exclusion criteria. The inclusion criteria for this study were patients between the ages of 18 and 89 years with a documented alpha-gal or red meat allergy and an admission to a hospital in the Sentara Healthcare system. Documentation of these allergies is based on self-reporting upon admission to the healthcare system or witnessed allergic reaction while receiving care within the healthcare system. There were no exclusion criteria. The health system consists of 12 hospitals located in Virginia and northeast North Carolina, areas in which alpha-gal allergy is known to be endemic. The study was deemed to be exempt from review by the Eastern Virginia Medical School Institutional Review Board.

All patient visits meeting inclusion criteria were then manually reviewed for heparin product administration and alpha-gal reactions. Alpha-gal reactions were defined in this study as patient-specific reactions that were reported within progress notes in the EMR during visits. Common alpha-gal reactions such as pruritus, rash, swelling, shortness of breath, nausea, vomiting, and diarrhea were classified as suspected alpha-gal reactions. A more thorough review of records was undertaken for any patient on whom the heparin product was held or discontinued at any time after initiation, as an associated allergic reaction could have been the reason for the hold/discontinuation. Alpha-gal antibody titers were not routinely drawn; therefore, an adverse drug reaction probability scale was used for association of the reaction with the heparin product. (Naranjo et al., 1981) A score correlating to probable or definite was considered an associated reaction. Alpha-gal reactions were analyzed as an incidence rate across all visits in which a patient received a heparin product. Descriptive statistics were used to characterize the study population.

Results

There were 133 patients with a documented alpha-gal allergy in the hospital system. The population was 60% female with a median age of 62. Patient demographics are shown in table 1. Patients with an alpha-gal allergy received a heparin product in 57 of 158 hospital visits (36.1%). The most common dose of UFH administered was 5000 units

Table 1
Baseline characteristics.

Demographics	No. of patients (%) (N = 133)
Median age (IQR)	62 (48–75)
Gender	
Female	80 (60%)
Race	
Caucasian	109 (82%)
African American	16 (12%)
Hispanic	4 (3%)
Other	4 (3%)
Geographical Location by Hospital	No. of visits (%) (N = 158)
Sentara Martha Jefferson Hospital; Charlottesville, VA	95 (60%)
Sentara Williamsburg Regional Medical Center; Williamsburg, VA	19 (12.5%)
Sentara Norfolk General Hospital; Norfolk, VA	16 (10%)
Sentara RMH Medical Center; Harrisonburg, VA	8 (5%)
Sentara Obici Hospital; Suffolk, VA	6 (4%)
Sentara Virginia Beach General Hospital; Virginia Beach, VA	5 (3%)
Sentara CarePlex Hospital; Hampton, VA	4 (3%)
Sentara Leigh Hospital; Norfolk, VA	4 (3%)
Sentara Albemarle Medical Center; Elizabeth City, NC	1 (1%)
Sentara Halifax Regional Hospital; South Boston, VA	0 (0%)
Sentara Northern Virginia Medical Center; Woodbridge, VA	0 (0%)
Sentara Princess Anne Hospital; Virginia Beach, VA	0 (0%)

twice daily. The most common dose of enoxaparin administered was 40 mg daily. The most frequent indication for a heparin product was venous thromboembolism prophylaxis. Heparin product administration details are shown in table 2.

Heparin products were tolerated in 56 of the 57 visits (98.3%). The incidence of an alpha-gal reaction to UFH was 2.6% (1/39) while the incidence of an alpha-gal reaction to enoxaparin was 0% (0/22).

Table 2
Occurrence of heparin administration during hospital visits.

	Result, N (%)
Number of visits in which a patient with a documented alpha-gal allergy received at least one heparin product	57 visits
Indication	
Prophylaxis dosing	53 visits (93%)
Treatment dosing	4 visits (7%)
Heparin product(s) administered	
Heparin only	37 visits (64.9%)
Enoxaparin	20 visits (35.1%)
Heparin and Enoxaparin	2 visits (3.5%)
Primary Outcome	
Any alpha-gal reaction to a heparin product (N = 57)	1 visit (1.75%)
Reaction due to treatment with heparin (N = 39)	1 visit (2.56%)
Reaction due to treatment with enoxaparin (N = 22)	0 visits (0%)
Secondary Outcomes	
Dosage	
Median daily dose of heparin administered (IQR)	15,000 units (10,000–15,000)
Median daily dose of enoxaparin administered (IQR)	40 mg (40–80)
Special Considerations	
Patient refusal of heparin product	6 visits
Documented history of tick bite in medical record	5 visits
Documented positive alpha-gal antibody labs prior to hospital visit (N = 8)	10 visits
Median antibody level, kU/L (IQR)	11.79 (0.90–26.6)
Median days between antibody lab and hospital visit (IQR)	450 (148–882)

The single patient who experienced an alpha-gal reaction was a 54-year-old male who received two doses of UFH 5000 units subcutaneously for venous thromboembolism prophylaxis. After the second dose, the patient noted papules under his eyes, which he reported as similar to previous presentations of his alpha-gal allergy. UFH was subsequently discontinued six hours after the second dose, and a progress note describing the reaction was documented in the EMR. No further treatment or escalation in care was needed to manage his allergic reaction. The patient was discharged the next day. Five months prior to this hospital stay, the patient had reported hives after eating pork and beef and was subsequently tested for an alpha-gal allergy. His tests were completed 147 days before the hospital admission and resulted positive for alpha-gal IgE antibodies (24.20 kU/L, non-allergic reference range < 0.10 kU/L) with all antibody subsets also positive (beef IgE, lamb/mutton IgE, and pork IgE). This patient's antibody level was one of the highest among patients who had previously received a test for antibodies within the study population. It is unknown if he had experienced a previous tick bite.

Geographically, 95 visits that involved a patient with a documented alpha-gal allergy in the Sentara Healthcare system occurred at Sentara Martha Jefferson Hospital in Charlottesville, VA (Fig. 1). Documentation of a history of tick bite was explicitly noted in the medical record during only 5 visits.

Discussion

The incidence of alpha-gal reaction to UFH within this study was 2.6%, suggesting that this drug does have the potential to induce an alpha-gal reaction. No such reaction was documented in patients receiving enoxaparin in this study, which may indicate that this product is less associated with alpha-gal reactions. To our knowledge, there have been no published case reports of alpha-gal reactions specifically associated with any LMWH. It is difficult to draw conclusions about the reactogenicity of these products in this population given the small sample size of enoxaparin-treated patients in the present study; however, based on the data, it may be reasonable to avoid UFH in patients with a known alpha-gal allergy when treating for indications for which enoxaparin could be reasonably substituted.

Additionally, the finding that 60% of visits occurred in the central Virginia city of Charlottesville suggests that additional monitoring or alternative agents may be necessary in this area to avoid the risk of triggering a reaction. This finding is supported by a cohort study out of Charlottesville. (Hawkins et al., 2020) In terms of geographic location,

the high prevalence of individuals with an alpha-gal allergy in central Virginia can be correlated with the increasing population of the Lone Star tick, *Amblyomma americanum*, in the southeastern United States. In central Virginia, 97.0% of patients presenting to a healthcare setting with delayed anaphylaxis to red meat had alpha-gal antibodies. (Commins et al., May) The prevalence of this reaction is higher than in areas of the country where tick bites are rare. (Commins et al., May) While analyzing the incidence of alpha-gal reactions in this population, a questionnaire assessing the relationship between history of tick bites and serum IgE antibody levels showed that greater than 90% of the subjects with serum IgE antibodies to alpha-gal reported a history of tick bites. (Commins et al., May) The incidence of alpha-gal in the area could also be explained by the various amount of activities that could expose an individual to a tick bite such as walking in grassy areas for hikes, hunting, and riding through thick vegetation.

To our knowledge, this observation is the first study to investigate the incidence of alpha-gal reactions in response to both UFH and LMWH administration. There have been very few studies, mainly limited to case reports and case series, examining the impact of heparin products on triggering an alpha-gal reaction. The largest cohort study was performed in 17 patients with a known alpha-gal allergy who all underwent cardiac surgery and received high-dose UFH. (Hawkins et al., 2020) The findings from this cohort suggested that high antibody titers (i.e. >50kU/L) may help differentiate those in whom an alpha-gal reaction may or may not be expected. (Hawkins et al., 2020) The authors of the Charlottesville study recommended measurement of pre-operative alpha-gal titers in cardiothoracic surgery patients with suspected alpha-gal allergy prior to use of high-dose UFH. (Hawkins et al., 2020) In contrast, the patient in our study who experienced a reaction to UFH had recently demonstrated a lower antibody titer and also received a lower heparin dose than the patients described in this cohort, suggesting that titers may fluctuate over time and/or may not be the best predictor to use for risk assessment.

The difference in observed incidence rates between UFH and enoxaparin in this study could be explained through variance of the inoculant, alpha-gal. LMWHs are produced through an enzymatic depolymerization of UFH resulting in anticoagulants with smaller-sized sugar residues. Due to this manipulation, LMWHs are less similar to the natural porcine or bovine product, UFH. This manipulation also confers a lower risk for another known immune-mediated reaction to heparin products, heparin-induced thrombocytopenia (HIT). Compared with UFH, the estimated incidence of HIT with LMWHs is about ten-fold lower (0.2% vs. 2.0–3.0%) due to a less efficient interaction with

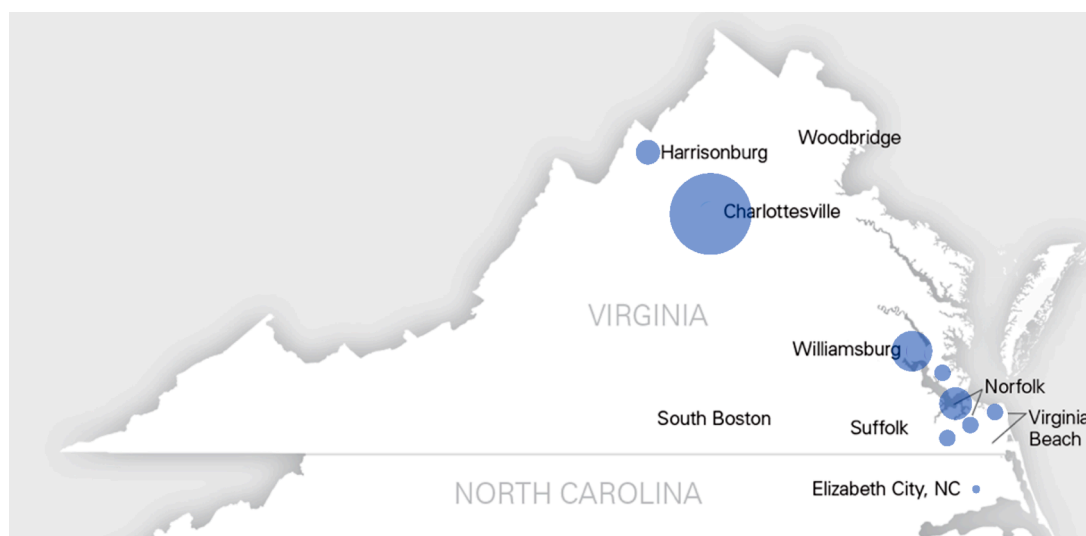


Fig. 1. Relative locations of reported alpha-gal allergies across one hospital system in Virginia and North Carolina.

heparin-platelet factor 4 and platelets. (Hawkins et al., Jul; Chandarajoti et al., 2016; Walenga et al., Feb;30)

Mawhirt and Banta described a patient with an alpha-gal anaphylaxis history who tolerated porcine-derived UFH during a preoperative procedure, but also noted the uncertainty of risk with heparin administration in the alpha-gal patient population. (Mawhirt and Banta, 2019) Crow et al. described a patient with an alpha-gal allergy who developed abdominal pain and a small bowel ileus immediately after receiving intravenous UFH. (Crow et al., 2019) Mozzicato et al. emphasized the need to evaluate the risk of anaphylaxis in required porcine or bovine valve replacements after two patients with an alpha-gal allergy experienced hypersensitivity reactions. (Mozzicato et al., 2014) Other studies have examined the management of anticoagulation for cardiac surgeries in patients with alpha-gal allergies. (Kleiman et al., 2017; Naranjo et al., 1981) More recently, mammalian valve degeneration has been reported in patients with alpha-gal IgE, which suggests implications for management of patients with alpha-gal allergy that extend beyond medication administration. (Arepally and Ortel, 2010; Sell-Dottin et al., 2017)

Aside from high doses of heparin products, pharmaceutical products made with only small quantities of animal-derived excipients may also cause allergic reactions, making avoidance of potentially immunogenic antigens particularly challenging. For example, products with magnesium stearate, such as acetaminophen produced by McNeill McKesson, hydromorphone injection by Hospira, and pregabalin by Pfizer, have all been placed on a caution list for use in patients with an alpha-gal allergy due to their potential mammalian-derived contents. (Dunkman et al., 2019) However, a risk-versus-benefit assessment may also deem the medication necessary based on the clinical situation. It is imperative to note that manufacturers are not required to report the potential alpha-gal content of their drugs, so it may be difficult to assess whether a medication containing one of these animal-derived excipients has a higher risk of inducing a reaction.

Due to the retrospective nature of this study, we had limited data on the history of tick bites and dietary intake for each patient in our study population. Furthermore, the timeframe of reactions could have resulted in underreporting within the medical record. All patients are asked about allergies upon admission; however, we are unable to determine whether any patients' self-reported red meat allergies may have instead been due to a dietary preference, rather than a true allergy. Likewise, we are not able to conclude why an individual might have refused a heparin product if it was not explicitly noted in the medical record. Reactions may be delayed up to 3–6 h, and the medical record is only available for events that occur within the hospital or are noted in hospital-owned clinics. The nature of non-anaphylactic alpha-gal reactions, such as nausea and vomiting, may have been misattributed to other causes. However, we made sure to thoroughly review all patients who received a heparin product, with special attention to any heparin order that was discontinued or any patient who received medications commonly used for allergic reactions (e.g. epinephrine, steroids), as a possible signal for an adverse reaction. Serologic testing was not conducted on each visit, which may have resulted in a lower number of reported alpha-gal reactions. Although our study involved multiple hospitals, these hospitals are within a single healthcare system in a limited geographic region, so results may not be broadly applicable to other areas. Lastly, the relatively small sample size of this study limited our ability to assess the association between heparin product, dose, or duration of treatment to the likelihood of reaction. Nonetheless, this study is the largest to date to investigate the incidence of alpha-gal reactions with the use of high and low-dose heparin products.

Conclusion

In this observational study, heparin products were associated with a low incidence of alpha-gal reactions among patients with documented

alpha-gal allergy. It is possible that enoxaparin poses less of a risk for reaction in these patients compared to UFH. As this is the largest study of its kind, additional studies are needed to fully elucidate the risks associated with use of these agents in patients with alpha-gal allergy.

Declaration of Competing Interest

None of the authors have any financial conflicts or otherwise to disclose. There was no funding for the completion of this study.

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