

Case Report

Heparin desensitisation prior to cardiopulmonary bypass in a patient with alpha-gal allergy

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Summary

This case report describes the implementation of a heparin desensitisation strategy for a patient with confirmed galactose-alpha-1,3-galactose (alpha-gal) allergy, prior to cardiac surgery. We describe the pre-, intra- and postoperative management. We believe this report can enhance the limited data currently in existence on alternative strategies for heparin utilisation in cardiopulmonary bypass in a previously intolerant patient population.

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Introduction

Drug allergies are commonly encountered in the peri-operative setting. Usually, drugs can be avoided when alternatives are available or when the drug is not essential. However, challenges arise when the drug effect is essential, such as high dose heparin anticoagulation for cardiopulmonary bypass (CPB). The only alternative drugs (argatroban and bivalirudin) require important modifications to standard CPB while also posing an increased risk for both bleeding and thrombotic complications [1]. Patients who have an allergy to galactose-alpha-1,3-galactose (alpha-gal) – an oligosaccharide present on glycoproteins and glycolipids in most non-primate mammals – may develop potentially life-threatening anaphylaxis when exposed to heparin [2]. Reactions can occur within minutes of exposure and minimal amounts of the drug can induce severe reactions in highly sensitised individuals [3]. Desensitisation to an allergen was first reported in 1911 by Noon; since then, the practice of allergen immunotherapy is now supported by well-controlled studies [4]. Here, we describe a case where a patient with a documented alpha-gal allergy, including a prior heparin hypersensitivity reaction, successfully underwent heparin desensitisation immediately prior to cardiac surgery.

Report

A 67-year-old man with a past medical history of coronary artery disease (CAD) and alpha-gal syndrome presented with newly diagnosed gastric adenocarcinoma. During workup for gastrectomy, he was found to have multivessel CAD requiring surgical revascularisation.

Two years earlier, after a tick bite, the patient developed recurrent delayed onset facial and tongue angioedema with hives and breathing difficulty after ingesting beef or other mammalian meat products. He was seen by an allergist who diagnosed alpha-gal allergy. He recently described developing hives immediately after his chemotherapy port was flushed. Presumably, his port would have been 'locked' with heparinised saline since that is standard practice at our institution. He stated they avoided

this with subsequent sessions, and he did not develop any further reactions. His most recent records indicated IgE titres were checked five months earlier showing: beef IgE = 4.58 kU.l^{-1} ($3.91\text{--}19 \text{ kU.l}^{-1}$ very high), pork IgE = 0.73 kU.l^{-1} ($0.56\text{--}1.4 \text{ kU.l}^{-1}$ moderate) and alpha-gal specific IgE = 27.60 kU.l^{-1} (positive titre $> 0.1 \text{ kU.l}^{-1}$). This test for alpha-gal specific IgE was developed, and its performance characteristics determined by Eurofins Viracor (Lenexa, KS, USA). However, it has not been approved by the U.S. Food and Drug Administration.

The recent reaction to heparin and elevated IgE levels suggested continued sensitisation to alpha-gal and mammalian products. Thus, the patient was considered high risk for anaphylaxis to i.v. heparin required for CPB.

Our allergy and immunology service recommended pre-operative heparin desensitisation therapy prior to surgery. The patient consented to undergo rapid desensitisation using an institutional protocol previously developed and approved by our Pharmacy and Therapeutic Committee, specifically for heparin allergic patients. Per this protocol, the patient was commenced on twice daily oral famotidine 20 mg and cetirizine 10 mg upon admission to the Intensive Care Unit (ICU), until surgery.

On the evening prior to surgery, the patient was admitted to the cardiac surgical ICU to undergo desensitisation. The patient completed the desensitisation protocol (Table 1), without any adverse reactions such as itching, rashes, facial or airway swelling. No steroids were administered at any point to avoid masking early signs of hypersensitivity reaction [5]. After desensitisation, he was continued on a heparin infusion with a target activated partial thromboplastin time of 40–60 s until he was fully heparinised for CPB. Heparinisation for bypass was achieved with an initial bolus of 30,000 IU of unfractionated heparin, and two additional boluses of 5000 IU to achieve an activated clotting time (ACT) of 462 s (our institutional ACT goal is $> 400 \text{ s}$). A single dose of diphenhydramine 50 mg i.v. was co-administered at the time of intraoperative heparinisation.

The patient was separated from bypass on an i.v. infusion of noradrenaline $4 \mu\text{g.min}^{-1}$, and heparin was fully reversed with a total of 300 mg of i.v. protamine in divided doses to normalise the ACT and restore haemostasis prior to chest closure. Upon arrival in the ICU, 90 min after protamine, the patient was commenced on heparin 5000 IU subcutaneously every 8 h to prevent resensitisation (Fig. 1). This was done as a preventative measure in case the patient suffered a complication that required re-exposure to heparin. He remained on this until he was discharged on the fifth postoperative day. His postoperative course was unremarkable, never experiencing urticaria, hives, or facial or tongue angioedema.

Discussion

Anaphylaxis to heparin in patients allergic to alpha-gal is a well described but rare allergy, occurring in as few as 1% of patients who undergo cardiac surgery in the United States [2]. The global incidence of alpha-gal allergy is not well understood. Because this condition was first described in patients in the southeast United States in 2008, testing and documentation is still inconsistent [6]. It has been reported that people who live in regions where tick bites are prevalent have much higher rates of IgE antibodies to alpha-gal [7], with regions such as rural Africa (100 of 131 tested patients) and Ecuador (110 of 295) also reporting a high prevalence. Regions such as Denmark (612 of 2100) and Sweden (1 of 150) have much lower prevalence [7]. A small number of individual case reports describe successful use of heparin during cardiac surgery following pre-treatment with various steroid and antihistamine combinations [8]. However, in 2021, Hawkins et al reported a 24% incidence of severe anaphylaxis to heparin during cardiac surgery in patients with alpha-gal allergy despite pre-treatment with antihistamines and steroids [2]. At the time of writing, there are no consensus guidelines to help direct clinical care in this setting.

The risk for anaphylaxis during cardiac surgery in a patient with alpha-gal allergy is particularly high. This is because both risk of reaction and severity are determined by the antigen dose and route of administration, which is greatest with i.v. administration [9]. During cardiac surgery, very large doses of i.v. heparin are rapidly administered immediately prior to CPB. Indeed, many of the reported severe reactions to heparin occurred in this setting [9].

Unfortunately, the alpha-gal content in heparin formulations varies depending on the manufacturer and is not routinely reported. Skin testing prior to administration has therefore been proposed as a quick method to determine the risk for reaction; however, this method has yielded inconsistent results [9].

An alternative approach for patients with IgE-mediated drug reactions is to induce a temporary tolerance to the drug through rapid desensitisation (also referred to as cluster or rush desensitisation) immediately prior to administering the therapeutic dose. Rapid desensitisation is typically performed over several days, but ultra-rapid (ultra-rush) protocols performed over hours are also used [10]. Rapid desensitisation protocols have also been developed where the therapeutic dosage can be administered within a few hours and they have become an important component in the management of immediate

Table 1 Protocol for rapid heparin desensitisation in a patient with alpha-gal allergy. Patient must be in an intensive care unit with continuous monitoring and 1:1 nursing. An anaphylaxis kit is kept at the patient bedside throughout the process. IU, international units.

Dose #	Bag #	Time (H:MM)	Rate (ml.h ⁻¹)	Volume to be infused (ml)	Dose given (IU)	Rate (IU.h ⁻¹)	Cumulative dose (IU)	Infuse for	Time to monitor patient before moving to next dose
Start with bag #1, which is 5 units of unfractionated heparin in 250 ml 0.9% sodium chloride									
1	1	0:00	4 ml.h ⁻¹	1 ml	0.02	0.08 IU.h ⁻¹	0.02	15 min	0 min
2	1	0:15	8 ml.h ⁻¹	2 ml	0.04	0.16 IU.h ⁻¹	0.06	15 min	0 min
3	1	0:30	16 ml.h ⁻¹	4 ml	0.08	0.32 IU.h ⁻¹	0.14	15 min	0 min
4	1	0:45	32 ml.h ⁻¹	8 ml	0.16	0.64 IU.h ⁻¹	0.3	15 min	0 min
Change to bag #2, which is 50 units of unfractionated heparin in 250 ml 0.9% sodium chloride									
5	2	1:00	6.4 ml.h ⁻¹	1.6 ml	0.32	1.28 IU.h ⁻¹	0.62	15 min	0 min
6	2	1:15	12.8 ml.h ⁻¹	3.2 ml	0.64	2.56 IU.h ⁻¹	1.26	15 min	0 min
7	2	1:30	25.6 ml.h ⁻¹	6.4 ml	1.28	5.12 IU.h ⁻¹	2.54	15 min	0 min
8	2	1:45	51.2 ml.h ⁻¹	12.8 ml	2.56	10.24 IU.h ⁻¹	5.1	15 min	0 min
Change to bag #3, which is 500 units of unfractionated heparin in 250 ml 0.9% sodium chloride									
9	3	2:00	10.2 ml.h ⁻¹	2.55 ml	5.1	20.4 IU.h ⁻¹	10.2	15 min	0 min
10	3	2:15	20.5 ml.h ⁻¹	5.125 ml	10.25	41 IU.h ⁻¹	20.45	15 min	0 min
11	3	2:30	41 ml.h ⁻¹	10.25 ml	20.5	82 IU.h ⁻¹	40.95	15 min	0 min
12	3	2:45	81.9 ml.h ⁻¹	20.475 ml	40.95	163.8 IU.h ⁻¹	81.9	15 min	0 min
13	3	3:00	163.8 ml.h ⁻¹	40.95 ml	81.9	327.6 IU.h ⁻¹	163.8	15 min	0 min
Change to bag #4, which is 5000 units of unfractionated heparin in 250 ml 0.9% sodium chloride									
14	4	3:15	32.7 ml.h ⁻¹	8.175 ml	163.5	654 IU.h ⁻¹	327.3	15 min	0 min
15	4	3:30	50 ml.h ⁻¹	50 ml	1000	1000 IU.h ⁻¹	1327.3	60 min	0 min
Total time to desensitise ≈ 4 h, 30 min									
Total cumulative dose in desensitisation = 1327.3 IU of unfractionated heparin									
If patient successfully tolerates desensitisation begin maintenance dosing									

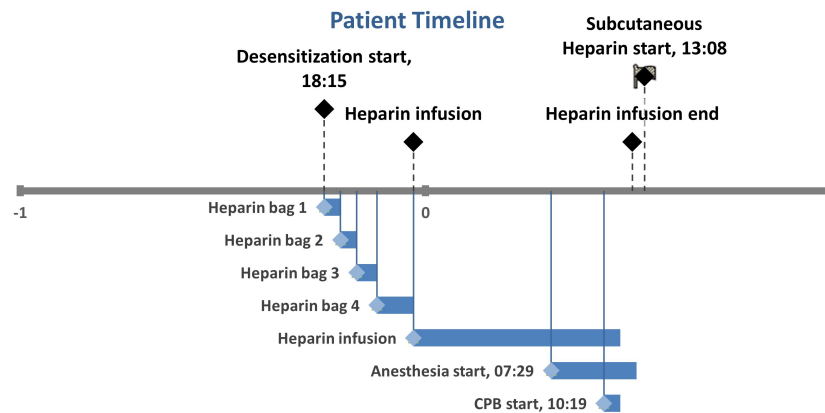


Figure 1 Timeline of heparin administration.

hypersensitivity reactions [4]. While concern has been expressed regarding the risk of inducing anaphylaxis in patients with severe uncorrected CAD, reactions that occur during desensitisation are usually mild and able to be managed [8].

We prepared a 4-h and 30 min protocol consisting of four solutions of drug delivery. The first solution was started at approximately 1/10,000th of the final dose of heparin in IU.h⁻¹ in a provocation test. The dose was doubled in 15-min intervals until the target heparin infusion rate was reached (Table 1). Subsequently, once the desensitisation portion of the protocol was completed without complication, a standard heparin infusion at a maintenance rate was continued until surgery.

The case presented here, and our subsequent experience, suggest that heparin desensitisation should be considered in alpha-gal allergic patients prior to cardiac surgery. This report highlights that a thorough patient review and initiation of a rapid desensitisation protocol can lead to minimal delays to surgery and the ability to then proceed to CPB without the concern of a severe reaction occurring. The risks for severe reactions during desensitisation in a highly controlled environment appear to be minimal, and without desensitisation, the risk for severe reactions even when pre-treated with antihistamines and steroids remains unpredictable. Prospective studies in this patient population are warranted for future treatment guidelines to be established.

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