

A role for vancomycin epicutaneous skin testing in the evaluation of perioperative anaphylaxis

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Clinical Implications

- Vancomycin epicutaneous skin prick testing (SPT) has not been validated, and its role in evaluating vancomycin hypersensitivity reactions is not well defined. We present a case that illustrates the utility of vancomycin SPT in the evaluation of perioperative anaphylaxis and demonstrate that 50 mg/mL is a nonirritating concentration for epicutaneous skin testing.

TO THE EDITOR:

Perioperative anaphylaxis is a life-threatening hypersensitivity reaction (HSR). It has been estimated to occur in 1:3,500 to 1:20,000 procedures with a mortality rate of up to 9%.¹ Identifying the causative agent is crucial to avoid re-exposure and prevent subsequent untoward outcomes. Antibiotics have been identified as the most common cause of perioperative HSR.² Vancomycin is one of a limited number of antibiotics that are FDA-approved for use in perioperative antimicrobial prophylaxis.³

Vancomycin HSR can be attributed to nonspecific direct mast cell stimulation ("red man syndrome")⁴ or type I HSR (IgE-mediated mast cell activation). Currently, the utility of skin testing in evaluating vancomycin HSR is unclear. Epicutaneous skin prick testing (SPT) has not been investigated as a diagnostic test for vancomycin HSR, and intradermal testing has been associated with false positives at dilutions as low as 0.01 milligrams per milliliter (mg/mL).^{4,5} We present a case of perioperative anaphylaxis in which vancomycin SPT helped identify vancomycin as the culprit agent.

CASE

A 60-year-old woman with a history of heart disease and adrenal insufficiency on chronic prednisone 6 mg daily since 2008 developed *Enterococcus faecalis* bacteremia with presumed pacemaker infection that required treatment with gentamicin and ampicillin and pacemaker extraction. Two months after treatment, a hematoma developed at the site of pacemaker extraction and evacuation was recommended. Hematoma evacuation began at 7:44 AM. Chlorhexidine was used to clean the surgical site, and vancomycin 50 milligrams (mg) was given intravenously preoperatively. At 8:06 AM, intravenous propofol 100 mg and succinylcholine 100 mg were used for anesthesia induction. At 8:14 AM, the patient developed sudden onset of increased peak pressures, inability to ventilate, and profound hypotension (systolic blood pressure was 50 mm Hg) with erythematous, flushed skin. Bedside echocardiography showed a globally preserved biventricular function without effusion or

tamponade, and imaging was negative for tension pneumothorax. She was treated with intravenous epinephrine 900 µg, hydrocortisone 100 mg, intravenous diphenhydramine 50 mg, 6 puffs of an albuterol inhaler, and placed on an intravenous epinephrine drip. A tryptase level, drawn 45 minutes after the start of the HSR, was elevated at 69 nanograms per milliliter (ng/mL). A follow-up tryptase level, drawn 5 days after the event, was normal (7 ng/mL).

Given her suspected perioperative anaphylaxis, she was referred to Allergy/Immunology. Skin testing was performed 6 weeks after her HSR to all possible culprit medications: chlorhexidine, vancomycin, propofol, and neuromuscular blocking agents including succinylcholine. Skin testing was performed using validated, nonirritating skin testing concentrations reported in a previously published study from our institution.⁶ She was not taking medications that could interfere with skin testing results⁷ and had appropriate responses to histamine and saline controls, indicating that her skin test findings were interpretable. She had a positive skin test, defined as a wheal diameter at least 3 millimeters (mm) larger than the negative control, to vancomycin (wheal 10 mm/flare 35 mm) at the epicutaneous step (50 mg/mL). She had negative skin tests to the following medications: atracurium, cisatracurium, rocuronium, succinylcholine, propofol, and chlorhexidine. There was no latex exposure at the time of the reaction, and specific IgE testing for latex was negative.

To ensure the validity of the positive SPT for our patient, we performed SPT with the same concentration of vancomycin (50 mg/mL), histamine (6 mg/mL), and saline on 10 adult controls (Table 1) with no history of vancomycin reaction or exposure. SPT was performed with undiluted (50 mg/mL) vancomycin oral solution for all subjects within 1 hour of opening a 5 mL container. All subjects had no reaction to vancomycin SPT and appropriate responses to histamine and saline controls. None of the subjects (including our patient) had any history of reaction to the excipients contained in the oral solution. These findings support that our patient's positive vancomycin SPT at 50 mg/mL was likely a true positive result. Given her clinical history, elevated event tryptase, and positive vancomycin SPT at a nonirritating concentration (NIC), she was diagnosed with perioperative anaphylaxis due to vancomycin.

DISCUSSION

This patient's clinical history and elevated serum tryptase level supported a diagnosis of perioperative anaphylaxis.¹ Theoretically, a tryptase level could be elevated in both IgE-mediated HSR and nonspecific direct mast cell stimulation seen during vancomycin infusion. Interestingly, it has been shown that although serum histamine levels rise during vancomycin reactions due to nonspecific direct mast cell stimulation, serum tryptase levels stay unchanged.⁸ Furthermore, this patient's clinical history was consistent with perioperative anaphylaxis, indicating that her elevated tryptase was due to IgE-mediated HSR. A thorough investigation of all agents she received before the onset of her reaction revealed positive skin testing to vancomycin only, suggesting that vancomycin was the cause of her anaphylaxis.

TABLE I. Baseline characteristics of control subjects (n = 10)

Clinical characteristics	
Age (y)	32 (27-67)
Male sex (%)	40
Atopic (%)	50
Asthma (%)	10
Atopic dermatitis (%)	10
Allergic rhinitis (%)	50
Nonatopic (%)	50
Other drug allergy (%)	10

Age is presented as median (range).

Current guidelines recommend that vancomycin be considered for perioperative antimicrobial prophylaxis in patients with a known methicillin-resistant *Staphylococcus aureus* (MRSA) colonization, in patients at high risk for MRSA colonization, and at institutions with high rates of postoperative or surgical site MRSA infections.³ A diagnostic test to evaluate vancomycin HSR will become essential as the number of MRSA infections continues to rise in the United States,⁹ creating a growing need for vancomycin use in health care settings.

Identification of an appropriately sensitive NIC for SPT is a crucial first step toward accurate investigation and validation of vancomycin skin testing. A prior publication reported an NIC of 1 mg/mL for vancomycin SPT in 4 nonallergic patients, but did not investigate SPT as a possible diagnostic test in vancomycin-allergic patients.⁴ Furthermore, higher concentrations, provided they are nonirritating, are more likely to have a higher sensitivity. Our reported NIC of 50 mg/mL is 50 times more concentrated than the previously reported 1 mg/mL. SPT with higher concentrations was not performed, as 50 mg/mL is the highest concentration of vancomycin readily available.¹⁰

As this patient's vancomycin SPT was positive, subsequent intradermal testing was not performed. Although an intradermal NIC has previously been reported,¹¹ intradermal testing is considered less specific than SPT and would have added little, if any, diagnostic information.⁷ Additionally, intradermal administration of a culprit allergen has been associated with fatal anaphylaxis, and would have been unsafe given the severity of this patient's initial reaction.⁷

In summary, vancomycin skin testing can be part of the evaluation of vancomycin-associated HSR in select cases where the clinical history and tryptase level both support IgE-mediated anaphylaxis over nonspecific mast cell activation. This case demonstrates that 50 mg/mL is an NIC for SPT and illustrates a role for vancomycin skin testing in evaluating vancomycin-associated HSR. Future studies are needed to investigate the predictive value of vancomycin skin testing in a larger cohort of vancomycin-allergic subjects.

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No funding was received for this work.

Conflicts of interest: K. G. Blumenthal has received research support from NIAID (National Institute of Allergy and Infectious Diseases) (T32 HL116275). A. Guyer receives royalties from UpToDate; and has received payment for developing education presentations from MetroWest. The rest of the authors declare that they have no relevant conflicts.

Received for publication April 2, 2015; revised June 2, 2015; accepted for publication June 22, 2015.

Available online August 2, 2015.

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2213-2198

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<http://dx.doi.org/10.1016/j.jaip.2015.06.017>

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