

Patent blue anaphylaxis: case report

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Clinical Implications

- This case report of anaphylaxis to patent blue illustrates the difficulties of investigating a patient with intraoperative anaphylaxis and underlines the importance of a comprehensive immunoallergologic evaluation to try to identify the culprit drug and to exclude potential confounders

TO THE EDITOR:

Blue dyes have been increasingly used for staging breast cancer and melanoma.¹ Their administration in association with radioisotope-labelled albumin is with rates of identification of sentinel lymph nodes of 99%.¹ Patent blue V (PBV) is a member of the triarylmethane family,² which also includes isosulfan blue and methylene blue (MB). The former shares structural homology with PBV, which is responsible for some degree of cross reactivity.^{1,3} Most published studies on allergic reactions to blue dyes do not include any immunoallergologic evaluation. In studies in which this evaluation was performed, the incidence of PBV allergy was 0.5%.³ We describe the immunoallergologic study of a patient with intraoperative anaphylaxis to PBV.

CASE REPORT

The patient was a 46-year-old woman, with no personal or family history of atopy but with 2 previous episodes of pruritic maculopapular rash after β -lactam administration: the first at age 12, 15 minutes after intramuscular penicillin for tonsillitis, and the second at age 30, after administration of amoxicillin and acetaminophen for a lower respiratory infection. She has tolerated acetaminophen but has not taken β -lactam antibiotics since then. After a diagnosis of breast cancer, she had a mastectomy with lymphatic mapping with undiluted PBV and sentinel node biopsy. General anaesthesia was induced with midazolam, fentanyl, propofol, and rocuronium. Dexamethasone, cephazolin, and esomeprazole were also administered. Within 5 minutes after PBV administration, the patient presented severe hypotension and generalized urticaria. Administration of intravenous adrenalin, hydrocortisone, methylprednisolone, hydroxyzine, ranitidine, and intravenous fluids resulted in prompt reversal of the shock within 10 minutes.

She was referred for an immunoallergology workup 6 weeks later. Latex and muscle relaxant allergy were excluded by negative skin prick test (SPT) and intradermal test (IDT) results. β -lactam allergy was excluded by negative SPT and IDT results with penicilloyl polylysine, minor determinant mixture, penicillin, amoxicillin, and cephalosporins (including cephazolin). Furthermore, results of drug provocation tests with penicillin, amoxicillin and cephazolin were all negative. SPT and IDT

results with anesthetics (propofol, fentanyl), dexamethasone, and esomeprazole were negative. To investigate PBV allergy, we performed SPT with PBV 2.5%, followed by IDT with PBV 0.00025% (1:10,000 dilution). The patient manifested a positive late reaction to SPT (30 minutes) and an immediate positive reaction to IDT (20 minutes). Irritative reactions were excluded by using the same concentrations for SPT and IDT in 10 healthy controls, all with negative results.

To find an alternative dye, MB was tested. SPT with MB 1% and IDT with MB 0.0001% (1:10,000 dilution) results were both positive. Basophil activation test results performed for both PBV and MB 49 months after the reaction were negative. The patient was diagnosed with PBV anaphylaxis with possible cross reaction with MB.

DISCUSSION

Anaphylaxis is defined as a life-threatening systemic hypersensitivity reaction with a prevalence in the general population that ranges from 0.05% to 2%.⁴ The underlying mechanism of IgE-mediated anaphylaxis relies on degranulation of mast cells or basophils with release of preformed mediators after cross-linking of surface IgE molecules to an allergen.⁵ The incidence of perioperative anaphylaxis ranges from 1:6000 to 1:20,000 anaesthetic procedures.⁵ Muscle relaxants (58%), latex (20%), and antibiotics (13%) are the most common etiologic factors in anaphylactic reactions during anaesthesia.⁴

In view of the patient's history of maculopapular rash after β -lactam administration, anaphylaxis to cephazolin was suspected. Cross reactivity of penicillins and cephalosporins is well known and ranges from 2% to 38%,⁶ which makes it imperative to exclude cephalosporin hypersensitivity, along with allergy to any of the other drugs used in the perioperative period. This was achieved by negative skin tests as both skin prick tests and intradermal tests were performed. The immunoallergologic evaluation did not reveal allergy to any drugs used in the perioperative period. To investigate PBV allergy, an adaptation of the Haque protocol was used²: SPT with PBV 2.5% followed by IDT with PBV 0.00025%. The reported PBV allergy prevalence in series with more than 350 patients ranged from 0.28% to 1.10%.⁷ However, only a few of the studies describe allergologic evaluations with SPT and IDT, and report a prevalence of PBV allergy of 0.5%.³

Since the patient had positive SPT and IDT to PBV, an alternative blue dye was tested. The other blue dye available in Portugal is MB. MB is a rare cause of anaphylaxis, and it is structurally different from PBV,^{1,3} but SPT with MB 1% and IDT with MB 0.0001% results were also positive. Cross reactivity of PBV and MB is uncommon but has been described,^{1,2} however, the mechanisms are not fully understood. PBV binds proteins through their SO₃ group. This protein-dye complex has an affinity for lymph vessels and is large enough to be trapped in the sentinel lymph node. MB is smaller and has no sulfonic acid groups, which does not share the same mechanism but diffuses directly into blood capillaries after subdermal injection.^{8,9}

There have been numerous reports of refractory anaphylaxis treated with MB in the dose of 1.5 to 2 mg/kg.¹⁰⁻¹² This compound is a selective inhibitor of the nitric oxide cyclic guanosine monophosphatase pathway and is recommended in various

TABLE I. Drugs available in Portuguese drugstores with PBV (excipient) in their composition*

Drug name	Availability
Sterillium (BODE chemie GmbH, a company of the Hartmann Group, Hamburg, Germany)	Cutaneous solution
Flogoral (benzenamine) Angelini Farmacêutica, Lda Dafundo, Portugal	Mouthwash
Tantum Verde/Difflam (Angelini Farmacêutica, Lda Dafundo, Portugal)	Mouthwash
Tums (GlaxoSmithKline, London, UK)	Tablet
Clonix (clonixina) (Lusomedicamenta, Queluz de Baixo, Portugal)	Blister
Periogard (Colgate-Palmolive GmbH, New York, NY)	Mouthwash
Fluconazole	Blister
Prozac (fluoxetine) (Lilly, Indianapolis, Ind)	Blister
Maxius (Jaba Recordati, Porto Salvo, Portugal)	Mouthwash
Lansoprazole	Blister
Lovastatina (statin) (Jaba Recordati, Porto Salvo, Portugal)	Blister
Minocycline	Blister
Omeprazole	Blister
Ramipril	Blister
Triatec (ramipril + hydrochlorothiazide) (Sanofi SA, Paris, France)	Blister
Venlafaxine	Blister

*Information was provided by the Centro de Documentação e Informação de Medicamentos of the Associação Nacional das Farmácias, based on the analysis of the summary of the product characteristics available at <http://www.infarmed.pt/>.

position papers for treatment of anaphylaxis refractory to initial management, especially with patients with hypotension.^{11,12} Despite its use to reverse anaphylaxis, MB can also be responsible for allergic reactions because it is observed with other drugs used in the treatment of anaphylaxis, such as antihistamines and corticosteroids. To investigate the potential mechanisms involved, basophil activation tests with both PBV and MB were performed, but the results were negative. However, the time elapsed between the reaction and this evaluation might be responsible for the negative results.

The underlying mechanism of PBV allergy is not fully understood. An IgE-mediated mechanism is suggested because SPT and basophil degranulation test results are frequently positive,^{1,13} and an increase in serum tryptase levels has been observed in cases of anaphylaxis.^{1,13} In their study of 9 patients with PBV allergy, Johansson et al¹³ proposed that PBV may behave as a hapten, which needs the conjugation to a carrier agent that could be a protein, sugar, or a lipid. However the same investigators were not successful in their attempt to characterize this PBV carrier.¹³ Furthermore, in most patients, the sensitization route is not immediately clear when considering that anaphylactic reactions usually occur on the first known exposure to the dye. The exposure and ensuing sensitization to this dye have been attributed to its utilization in everyday life items such as food (food coloring E131), cosmetics, color textiles, and drugs (Table I).^{1,2} The patient did not use any of the drugs listed in Table I, but it is difficult to exclude the remaining potential exposures.

Because no alternative dye was identified for future utilization, if the patient ever needs surgery with lymphatic mapping, then

preoperative prophylaxis could be suggested. Raut et al¹⁴ studied the effects of a protocol that used preoperative prophylaxis with hydrocortisone, diphenhydramine, and famotidine in the reduction of the incidence and severity of adverse reactions to isosulfan blue in 667 patients undergoing lymphatic mapping and sentinel lymph node biopsy.¹⁴ The investigators showed a small but not significant reduction in the incidence of adverse events with the prophylactic regimen and also a reduction in the severity of the reactions.¹⁴

In summary, this case report illustrates the difficulties of investigating a patient with intraoperative anaphylaxis and underlines the importance of a comprehensive immunoallergologic evaluation to try to identify the culprit drug and to exclude potential confounders.

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