



A case of immediate hypersensitivity reaction after an oral administration of patent blue dye

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Patent Blue V (PBV), also called E131 or Acid Blue 3 (CAS no. 3536-49-0), is commonly used in pharmacology, cosmetology, aesthetics, and food products. Hypersensitivity to this dye has been mainly described during sentinel lymph node procedures in patients with cancer.¹ Hypersensitivity reactions include urticaria, "blue hives," pruritus or generalized rash, extracutaneous lesions such as angioedema,^{1,2} bronchospasm, or cardiovascular symptoms.³ These are usually triggered after intravenous or subcutaneous exposure to PBV.⁴ Herein, we report, to the best of our knowledge, the first case of immediate hypersensitivity to PBV occurring after oral intake.

CASE REPORT

A 51-year-old woman with breast cancer experienced an immediate hypersensitivity reaction with superficial giant urticaria during a sentinel lymph node surgery using PBV (Bleu Patente V sodique 2.5%;

Laboratory Guerbet, Aulnay-sous-Bois, France) for lymph node mapping. Skin prick tests and intradermal tests with the products used during general anesthesia, cefuroxime as antibiotic prophylaxis, disinfectants, and latex were all negative. A prick test with undiluted PBV (25 mg/mL) was negative, whereas an intradermal test with PBV (dilution 1:10) was positive (Figures 1 and 2). We also prick tested methylene blue (5 mg/mL) and intradermally tested it (dilution 1:10). Skin tests to methylene blue were negative. Basal tryptase was normal. Of note, our patient recalled an episode of urticaria 10 years earlier after oral intake of paracetamol (Doliprane 500 MG) and a skin rash after oral intake of Lysocline (methacycline hydrochloride). Skin tests including prick tests, intradermal reaction, and patch tests to injectable form of paracetamol and doxycycline were negative at the time. Based on these results, we diagnosed an immediate hypersensitivity reaction to PBV, which was also relevant for her previous allergic reactions because paracetamol and Lysocline tablets also include PBV as excipient.



FIGURE 1 Wheal-and-flare reaction at skin test with patent blue (dilution 1:10 and undiluted, respectively)



FIGURE 2 Wheal-and-flare reaction at skin test with patent blue (dilution 1:10 and undiluted, respectively)

DISCUSSION

Vital dyes have been used for many years in a variety of clinical situations. Two types of blue dyes, PBV and methylene blue, are commonly used. Hypersensitivity has been described to both and to a PBV isomer, isosulfan blue, which are mainly used for lymph node mapping during sentinel lymph node surgery.⁴ Methylene blue is also used to prevent hepatopulmonary syndrome after liver transplantation and for virus attenuation of labile blood products.

The reported estimated incidence of allergic reactions to PBV varies widely between 150 and 1000 per 1 000 000 administrations.^{1,3,5-7} In an international multicenter phase III trial evaluating intraoperative lymphatic mapping and sentinel node biopsy in patients

with early stage melanoma, the incidence of allergic reactions to the blue dye was 0.17% (2 of 1173) and consisted of blue-colored urticaria. No patient developed an anaphylactic reaction to blue dye.⁸ In an 8-year survey of 1816 cases of anaphylaxis during anesthesia in France,⁹ the frequency of immediate reactions to PBV was 0.6%. However, in a study⁹ on 103 patients with immunoglobulin E (IgE)-mediated anaphylaxis during anesthesia, immediate hypersensitivity to PBV was suspected in 6% of patients. In a recent report⁵ of 266 cases of anaphylaxis collected over 1 year from all National Health Service hospitals, immediate hypersensitive reaction to PBV occurred in 4.5% of cases.

Besides its medical use, PBV (E131) is a substance used in everyday life and is structurally closely related to other triarylmethane dyes, which may be present in textiles, detergents, paints, cold remedies, cosmetics, and foods. Therefore, unnoticed sensitization to E131 may occur as in our case and hypersensitivity could arise after first exposure to PBV in surgery.¹⁰ In general, anaphylactic shock occurs within 10 min of the intravenous injection of the causative agent. This delay is slightly longer in the case of intradermal injection, ranging from 15 to 45 min.¹¹ Furthermore, the possibility of a secondary late-phase reaction to blue dye, if the initial administration resulted in a severe reaction, should be considered.²

The mechanisms of immediate hypersensitivity to PBV are still unknown. An IgE-mediated reaction was suggested based on the detection of IgE to PBV^{12,13} and increased tryptase levels, but a non-IgE-mediated reaction was also suggested.¹⁴ Our case highlights the importance of allergy skin testing. Both prick and intradermal tests have been proposed in the literature for the diagnosis of sensitization to blue dyes. The blue color of the papules is suggestive of the imputability of the dye. In a series of 14 clinical cases of dye-induced anaphylaxis, skin test results were positive in all patients when either prick or intradermal test was applied. However, in five patients prick test results were negative, while intradermal test results were positive.⁷ Intradermal tests should be thus performed in case of negative prick test results, as demonstrated in our observation.¹⁵ As PBV differs structurally from isosulfan blue and methylene blue, cross-reactivity is not expected. However, sensitization to both PBV and methylene blue has previously been reported.⁷ In conclusion, the possibility of occult hypersensitivity to PBV which may later manifest during sentinel lymph node surgery should be considered by dermatologists, surgeons, and anesthesiologists.

CONFLICTS OF INTEREST

None to declare.

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REFERENCES

1. Brenet O, Lalourcey L, Queinnec M, et al. Hypersensitivity reactions to Patent Blue V in breast cancer surgery: a prospective multicentre study. *Acta Anaesthesiol Scand*. 2013;57:106-111.
2. Iqbal FM, Basit A, Salem F, Vidya R. Feeling blue, going green and finding other attractive alternatives: a case of biphasic anaphylaxis to patent blue and a literature review of alternative sentinel node localisation methods. *BMJ Case Rep*. 2015;2015:bcr2015213107. <https://doi.org/10.1136/bcr-2015-213107>
3. Hunting AS, Nopp A, Johansson SG, Andersen F, Wilhelmsen V, Guttormsen AB. Anaphylaxis to Patent Blue V. I. Clinical aspects. *Allergy*. 2010;65:117-123.
4. King TA, Fey JV, van Zee KJ, et al. A prospective analysis of the effect of blue-dye volume on sentinel lymph node mapping success and incidence of allergic reaction in patients with breast cancer. *Ann Surg Oncol*. 2004;11:535-541.
5. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth*. 2018;121:159-171.
6. Lucas N, Interne SB, Laine P, Nicolie B, Fondrinier E. Anaphylactic shock due to patent blue: four case report and review of literature. *J Gynecol Obstet Biol Reprod*. 2010;39:116-120.
7. Mertes PM, Malinovsky JM, Mouton-Faivre C, et al. Anaphylaxis to dyes during the perioperative period: reports of 14 clinical cases. *J Allergy Clin Immunol*. 2008;122:348-352.
8. Morton DL, Cochran AJ, Thompson JF, et al. Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. *Ann Surg*. 2005;242:302-311.
9. Krishna MT, York M, Chin T, et al. Multi-centre retrospective analysis of anaphylaxis during general anaesthesia in the United Kingdom: aetiology and diagnostic performance of acute serum tryptase. *Clin Exp Immunol*. 2014;178:399-404.
10. Forschner K, Kleine-Tebbe A, Zuberbier T, Worm M. Type I sensitization towards patent blue as a cause of anaphylaxis. *Allergy*. 2003;58:457-458.
11. Dewachter P, Mouton-Faivre C, Benhaijoub A, Abel-Decollogne F, Mertes PM. Anaphylactic reaction to patent blue V after sentinel lymph node biopsy. *Acta Anaesthesiol Scand*. 2006;50:245-247.
12. Wöhr S, Focke M, Hinterhuber G, Stingl G, Binder M. Near fatal anaphylaxis to patent blue V. *Br J Dermatol*. 2004;150:1037-1038.
13. Johansson SG, Nopp A, Oman H, Stahl-Skov P, Hunting AS, Guttormsen AB. Anaphylaxis to patent blue V. II. A unique IgE-mediated reaction. *Allergy*. 2010;65:124-129.
14. Longnecker SM, Guzzardo MM, Van Voris LP. Life threatening anaphylaxis following subcutaneous administration of isosulfan blue 1%. *Clin Pharm*. 1985;4:219-221.
15. Haque RA, Wagner A, Whiskeen JA, Nasser SM, Ewan PW. Anaphylaxis to patent blue V: a case series and proposed diagnostic protocol. *Allergy*. 2010;65:396-400.

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