CASE REPORT
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A Case of Anaphylaxis to Patent Blue in a Patient with Sentinel Lymph Node Excision

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ABSTRACT

In medicine, patent blue violet (PBV) is utilized for staining lymphatic vessels in sentinel lymph node (SLN) surgery. Moreover, PBV (also called E131) is used as food additive.

We report on a 51-year-old non-atopic female with early breast cancer, who was scheduled for SLN excision and experienced an intra-operative anaphylactic reaction.

In diagnostics the skin prick test (SPT) was positive to PBV. Hypersensitivity reactions to PBV can arise after the first exposure in surgery as sensitization may arise from either PBV (E131) in foods (i.e. in sweets or blue curacao) or from other structurally closely related triarylmethane dyes in objects of everyday life like textiles, detergents, paints, cold remedies and cosmetics.

This article supports the necessity of an increased awareness of the possibility of anaphylactic reactions to PBV during SLN surgery, even if the patient never had contact to PBV before.

Keywords: Allergy; Anaphylaxis; Blue dye; Breast cancer; Patent blue violet; Sentinel lymph node excision; E131

INTRODUCTION

Patent blue violet (PBV), also known as food additive E131, is a dark blueish synthetic triphenylmethane dye mainly used as food colouring. In medicine, it is utilized for staining lymphatic vessels in sentinel lymph node (SLN) surgery. There are few reports on immediate

Type reactions to PBV, the first ones dating back to the early 1960's.[1]

This report is about a patient who received 6 mL of a 10% solution of alphazurine 2G (a blue triphenylmethane dye) intravenously. Immediately, she developed sneezing, respiratory distress, shock, convulsions, and temporary cardiac arrest.

CASE REPORTS

We report on a 51-year-old non-atopic female with early breast cancer who was scheduled for SLN excision. Following oral application of midazolam (Dormicum, Roche Pharma AG, Grenzach-Wyhlen, Germany) she received metamizole (Novalgin, Sanofi-

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Aventis Deutschland GmbH. Industriepark Höchst, Frankfurt, Germany), propofol (Disoprivan, AstraZeneca GmbH, Wedel, Germany) sufentanil (Sufenta, Janssen-Cilag GmbH, Neuss, Germany) and clindamycin (SOBELIN, Pfizer Deutschland GmbH, Berlin, Germany) intravenously. Shortly thereafter, PBV (Guerbet GmbH, Sulzbach/Taunus, Germany) was injected subcutaneously and within 45 minutes she developed generalized urticaria, angioedema, hypotension (80/40 mmHg) as well as bronchospasm. The reaction resolved after administration of prednisolone (Solu-Decortin H, Merck Pharma GmbH, Darmstadt, Germany), ranitidine (Ranitidin-ratiopharm, ratiopharm GmbH,Ulm, Germany), clemastine (Tavegil, Novartis Consumer Health GmbH, München, Germany), reproterol (Bronchospasmin, VIATRIS GmbH & Co. KG, Frankfurt am Main, Germany) and theophylline (Euphylong, ALTANA Pharma Deutschland GmbH, Konstanz, Germany). Due to unknown reasons and in contrast to existing guidelines, epinephrine was not applied by the treating physicians at that time.

At a follow-up visit in our allergy department six months later, there was no other history of hypersensitivity reactions or allergies. Total serum IgE was 26.9 kU/L and specific IgE to latex as well as serum tryptase levels, measured to rule out mastocytosis, were within normal range.

Skin prick test (SPT) was positive to PBV (Patentblau V 25 mg/mL, Guerbet GmbH) pure [5/30 mm; wheal/flare]; to diluted 1:10 in saline solution [5/30mm]; and negative at a dilution of 1:100 (Figure 1).

Intradermal tests (dilution 1:10) with metamizole, midazolam and clindamycin were negative as well as SPT with propofol and soy, an ingredient in propofol. Because of known histamine liberating effects of opioids, we did not perform skin tests with sufentanil.

Hypersensitivity to midazolam, metamizole and clindamycin was ruled out in our patient by well-tolerated titrated, single blind, placebo-controlled provocation tests. We therefore contributed the patient's reaction to PBV hypersensitivity. Any additional effect of sufentanil cannot be excluded.

In order to elucidate a supposed IgE-mediated mechanism to PBV, we performed sandwich enzyme-linked Immunosorbent Assay (ELISA) with serum from the allergic patient as well as from an atopic and one non-atopic controls. Sera were coupled to ELISA plates via an anti-human IgE antibody, which were afterwards incubated with PBV, followed by detection at 450 and 600 nm. We were able to detect a range of 500ng/ml down to 1.9ng/ml but did not obtain any signals when testing patient sera. Thus, even though positive SPT suggests an IgE-mediated mechanism, we were not able to detect specific IgE to PBV. Basophil Activation Test (Flow-CAST, Bühlmann, Schönenbuch, Switzerland) which investigates CD63 expression of sensitized basophils after incubation with PBV, was negative.

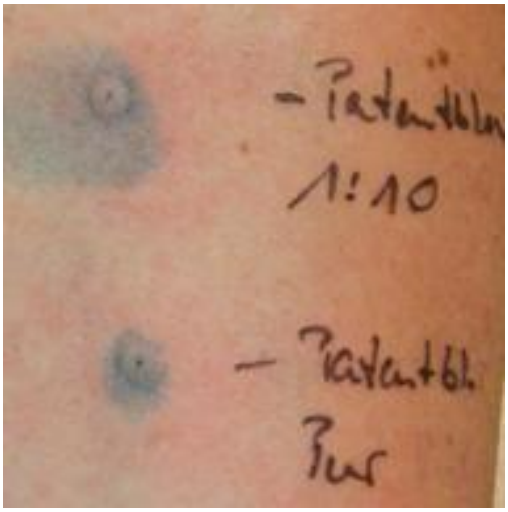

Figure 1. Wheal and flare reaction at skin prick test with patent blue (dilution 1:10, pure) in a patient with previous anaphylactic reaction to patent blue during sentinel lymph node excision.

DISCUSSION

Anaphylactic reactions during anaesthesia are reported to be mostly due to neuromuscular blocking agents, latex and antibiotics.[2] Some case reports and studies have also reported on blue dyes as cause of anaphylaxis (Table 1).

The reported rates of type-I-sensitization vary from 0.5% to 2.7%.[3-7] The present case highlights the importance of allergy skin testing. However; the irritating effect of PBV on the skin is quite subtle, therefore the negative predictive value of SPT with PBV is not 100%.[8] Considering the positive SPT in our patient, we did not perform intradermal test, which may be a valuable additional tool at a dilution of 1:100 in patients who are SPT negative.[9] The mechanisms of immediate-type reactions to PBV are still a matter of

Table 1. Incidences of allergic hypersensitivity to blue dyes

Reference	Incidence of hypersensitivity reactions			
	Type of study	Number of patients included	Incidence patent blue V / isosulfan blue	Severity of reactions *
(3)	retrospective	2392	0,6 to 2,7% (isosulfan blue)	Grade I 69% Grade II 8 % Grade III 23%
(4)	retrospective	161	6% (blue dyes)	-
(5)	prospective	1742	0,34% (patent blue V)	Grade I 67% Grade III 33%
(6)	prospective	371	1,1% (patent blue V)	Grade I 75% Grade III 25%
(7)	retrospective	1418	0,5% (patent blue V)	Grade I 29% Grade III 87% Grade IV 14%

Patent blue V: patent blue violet; * Ring and Messmer classification

research. An IgE-mediated reaction was proposed by Woehrl et al, who detected specific IgE to PBV and isosulfan blue using ELISA in a patient with history of anaphylaxis to PBV.[10]

Johansson et al. also detected an IgE-mediated mechanism in a patient with an anaphylactic reaction to PBV and proposed that; PBV bound to a protein, sugar or lipid, can serve as a hapten for an IgE complex.[11] By contrast, in our patient, no specific IgE to PBV was detectable. This is in accordance with investigations of Scherer et al.,[12] that did not detect specific IgE, but a positive BAT against isosulfan blue or PBV in a patient with history of immediate-type reaction to PBV. A non-IgE mediated reaction was also suggested.[13]

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 E131may occur and hypersensitivity reaction could arise after first exposure to PBV in surgery.[14,15]

Two alternatives to PBV for SLN mapping are isosulfan blue and methylene blue. Methylene blue is also known as methylene blue trihydrate or anhydrous methylene.[16] It is structurally not related to isosulfan blue or PBV, therefore no cross-reactivity is to be expected. In contrast, isosulfan blue is a structural isomer of PBV and may lead to cross reactions.[12] In summary, PBV and its isomer isosulfan blue are commonly used agents in sentinel node mapping in the surgical management of patients with cancer and may be responsible for intra-operative immediate-type hypersensitivity reactions. Whenever there is a clinical suspicion of anaphylaxis to PBV, the patient should be referred to an allergy specialist. To confirm the diagnosis skin allergy testing is useful.

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