

Blue dye allergy: Pitfalls in diagnosis and how to avoid them



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Clinical Implications

- Severe type I hypersensitivity reactions caused by blue dyes during sentinel lymph node biopsy are well described. The names of blue dyes are easily confused and unless the correct dye is tested, the diagnosis can be missed. We present 3 cases of incorrect dye identification highlighting the problem and suggest a protocol for systematic investigation.

TO THE EDITOR:

Misidentification and incorrect documentation of blue dyes used for sentinel lymph node biopsy (SLNB) could lead to devastating consequences. Dyes commonly used include patent blue V (PBV, Chemical Abstracts Service [CAS] number 3536-49-0), isosulfan blue (IB, CAS number 68238-36-8), and methylene blue (MB, CAS number 61-73-4).¹ Type I hypersensitivity reactions to both PBV and IB during SLNB are well described, but reactions to MB are extremely rare. We present 3 cases of incorrect dye identification and caution against these “near-miss” events.

A 52-year-old woman experienced intraoperative anaphylaxis during wide local excision (WLE) of a right breast lump and SLNB. According to the anesthetist’s referral, she developed a generalized rash, bradycardia (32 beats/min), and unrecordable blood pressure 18 minutes after induction with intravenous (IV) fentanyl, propofol, and atracurium and 10 minutes after IV amoxicillin-clavulanate. She was resuscitated with IV adrenaline, hydrocortisone, and chlorphenamine. Serial tryptase levels were 26.1 µg/L (1 hour), 29.9 µg/L (6 hours), and 3.4 µg/L (>24 hours). MB was documented in the drug list, but no further details were available. Comprehensive skin prick testing (SPT) and intradermal testing (IDT) results with all listed agents including MB 0.5% (Martindale Pharma, Woodburn Green, UK) were negative. The patient refused drug provocation tests. Her anesthetist was directly questioned regarding the possibility of a mislabeled dye. It transpired that PBV, not MB, was injected in the breast 15 minutes before cardiovascular collapse. Subsequent testing with undiluted PBV 2.5% (Guerbet, Aulnay-sous-Bois, France) yielded a positive SPT wheal of 7 mm and an IDT (1:10 dilution of PBV) with a 26-mm wheal with pseudopodia.

A 62-year-old woman, with a background of mild asthma, underwent WLE and SLNB for breast carcinoma. According to the anesthetic chart, subcutaneous MB and IV fentanyl, propofol, ondansetron, amoxicillin-clavulanate, and paracetamol were administered at induction. Forty minutes later she

developed widespread urticaria and bilateral wheeze. Vital signs remained stable. She received IV hydrocortisone and chlorphenamine. Serial tryptase levels were within normal limits. SPT/IDT results with other agents including MB were negative. However, after directly contacting the anesthetist, it was found that PBV was used instead of MB. SPT result with undiluted PBV 2.5% was negative, but IDT result with a 1:10 dilution was positive with a 10-mm wheal.

A 54-year-old woman underwent WLE of breast cancer. According to the anesthetic chart, propofol, fentanyl, paracetamol, and ondansetron were administered at induction followed by MB. Within 10 minutes, the patient developed hypotension (systolic blood pressure 40 mmHg), bronchospasm (SaO₂ 86% with loss of end-tidal CO₂ tracing), and flushing with generalized angioedema (larynx, face, and arms). Suxamethonium was given after the onset of the reaction to facilitate intubation. Hypotension did not respond to ephedrine/metaraminol. She required repeated boluses of IV adrenaline, hydrocortisone, and chlorphenamine and aggressive fluid resuscitation, which improved her blood pressure only after 30 minutes. Serial tryptase levels were 46 µg/L (1 hour), 22.6 µg/L (12 hours), and 6.5 µg/L (>24 hours). SPT/IDT results were negative to all agents including MB 1:1 and 1:10. On direct questioning, her anesthetist confirmed that PBV, not MB, was used. Indeed, SPT result was positive with a 5-mm wheal with undiluted PBV 2.5%, and a 4-mm wheal with at 1:10 dilution of PBV 2.5%. IDT was not performed.

Subsequently all 3 patients and their surgeons/anesthetists were advised to avoid PBV and IB in the future. MB was suggested a suitable alternative if a blue dye was needed again. Medical alert bracelets were also recommended.

PBV and IB have strong structural homology and cross-reactivity. Type I hypersensitivity reactions to both agents are well documented. MB has a comparable sentinel lymph node detection rate and is advocated as a “safer alternative” due to lower risk of systemic reactions. This however may only reflect its less frequent use, partly due to risk of local blue skin discoloration and necrosis, especially when injected superficially.²

Diagnosis of intraoperative anaphylaxis relies heavily on the accuracy of the referral letters and surgical and anesthetic records. Only after a comprehensive review of all available information can correct and appropriate investigations be instigated. A high level of clinical suspicion and acuity is of utmost importance when faced with unusual or negative results. Our cases were clinically suggestive of type I hypersensitivity/intraoperative anaphylaxis. The causative agent could have been any of the drugs given. However, after initial negative SPT/IDT results, the type of dye used was questioned, and incorrect documentation of PBV as MB occurred in all 3 cases. The correct diagnosis was then confirmed by further skin tests with PBV.

MB is less frequently used and hypersensitivity reactions are extremely rare. Indeed, we are aware of only a single convincing case of anaphylaxis during SLNB confirmed by SPT.³ Another report diagnosed allergy on the basis of positive IDT result with a known irritating 1:10 dilution of MB.⁴ Two further published case reports had either no or negative allergy investigations.^{5,6}

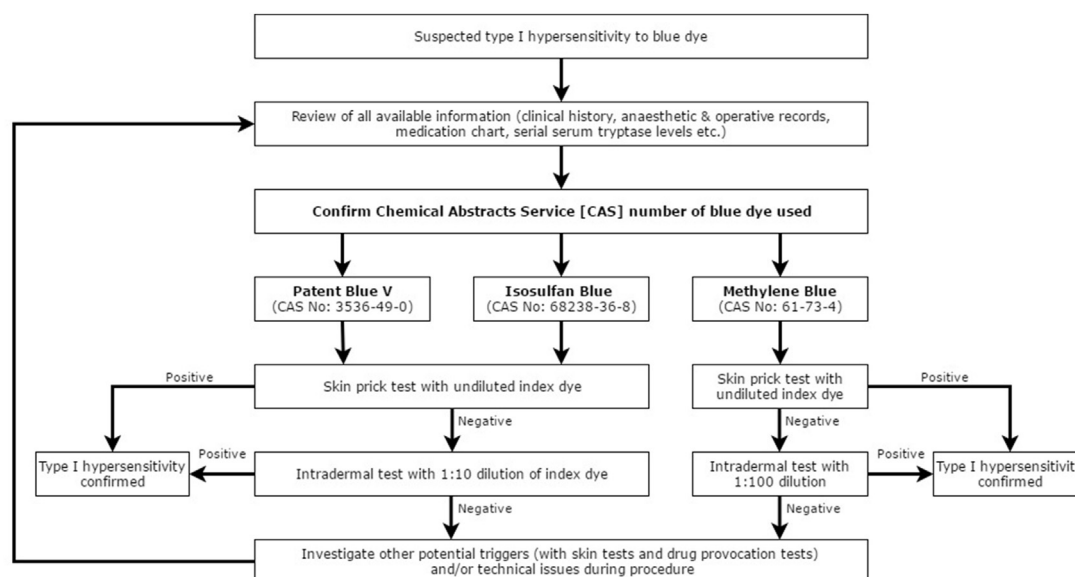


FIGURE 1. Protocol for investigation of suspected reactions to blue dye.

However, MB hypersensitivity has been reported in other clinical settings: after intrauterine instillation to assess tubal permeability and transfusion of MB-treated fresh frozen plasma.^{7,8}

We propose a new comprehensive algorithm for investigation of suspected blue dye allergy to avoid confusion and ambiguity (Figure 1). Incorrect diagnosis may have life-threatening consequences due to reexposure, unnecessary avoidance of medications, or redundant and costly exhaustive drug provocation testing to other drugs given concomitantly. A thorough assessment of perioperative anaphylaxis is required and we caution allergists/immunologists about the potential for misidentification of blue dyes. Furthermore, skin testing with incorrect (irritant) concentrations of MB increases the risk of skin necrosis, discoloration, and false-positive results. When a type I hypersensitivity reaction is suspected, a comprehensive review of all available records and confirmation of the correct dye by CAS number is imperative. Nonirritating concentrations for SPT and IDT of the index dye should be used.⁹ Increased physician vigilance and a multidisciplinary approach based on close communication with surgeons and anesthesiologists are crucial to avoid the misidentification of the culprit dye, which is a true “near-miss” or “never-event.”

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