



Patent Blue V dye anaphylaxis: experience of Australian and New Zealand surgeons

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Abstract

Background: Patent Blue V dye (PBVD) can cause severe anaphylaxis. For sentinel node biopsy (SNB) in breast cancer patients, controversy exists as to the utility of PBVD in addition to lymphoscintigraphy. This survey assessed Australian and New Zealand breast surgeons' experience of anaphylaxis with PBVD.

Methods: The survey was distributed to all 180 members of the BreastSurgANZ society in May 2011. Seventy-six (42%) current members responded. A retrospective analysis was performed on survey responses.

Results: Seventy-five members used PBVD on a median of 50 cases per year (0–250 cases per year) for a median of 10 years (4 months–15 years). Overall, 44 members (58.7%) experienced definite or possible allergic reaction to PBVD, but only 16 members (21%) witnessed severe anaphylaxis associated with a fall in blood pressure. Of the 34 members who experienced what they considered definite anaphylactic reactions with PBVD, only 18 members confirmed with allergy testing. The overall reported incidence of anaphylactic reactions of any severity was 0.15%. The median time to anaphylaxis was 20 min (0–90 min). Forty members (53.3%) reported routine discussion about PBVD risks as part of informed consent. Only seven members performed routine pre-op skin testing. Overall, 91% of the members accepted the rare but real risk of severe anaphylaxis and 76% did not question the additional value associated with its use.

Conclusion: Australian and New Zealand breast surgeons' reported that the anaphylaxis rate from PBVD was 0.15%. The majority of surgeons continued to use PBVD to facilitate SNB.

Introduction

Sentinel lymph node biopsy (SNB) is routinely used for accurate staging of breast cancer patients. In 2007, Cancer Australia (formerly National Breast and Ovarian Cancer Centre) performed a systematic review of trials and concluded with strong evidence that the combined use of lymphoscintigraphy with radio-isotope and blue dye lymphatic mapping resulted in statistically higher sentinel node detection and accuracy rates (98–100%) than either modality alone (blue dye alone 86–90% and radio-isotope alone 94–97%).¹ The National Institutes of Health and Clinical Excellence in the United Kingdom 2009 guideline also recommends that SNB should be performed using a combination of radio-isotope and blue dye

agents.² In Australia, Patent Blue V dye (PBVD) has been extensively used in surgical oncology, most often in breast cancer and melanoma surgery, and it is usually combined with ^{99m}Tc-labelled antimony sulphur colloid to achieve high sentinel node localization and biopsy rates. The alternative to a failed SNB is performing a staging level 1 and 2 axillary dissection, which has considerably more morbidity than SNB.^{3–6}

There is a known risk of anaphylaxis associated with PBVD use.⁷ The spectrum of adverse reactions from PBVD or other commonly used blue dyes such as isosulfan blue dye (ISBD) ranges from cutaneous manifestations, such as blue hives or wheals, to haemodynamic instability through to death from severe anaphylaxis.^{8,9}

Recently, controversial and provocative Australian literature was published, questioning the safety and utility of PBVD in routine breast cancer surgery.^{10,11} As a result of the publication of these articles, this survey was instigated to assess Australian and New Zealand breast surgeons' experience and attitudes towards the risk of anaphylaxis associated with PBVD use.

Methods

The lead author developed a questionnaire survey with review assistance from the current executive of Breast Surgeons of Australia and New Zealand Incorporated (BreastSurgANZ). At that time, BreastSurgANZ was a new society with 180 founding members. The survey was sent out electronically or handed in hardcopy to the full membership of BreastSurgANZ in May 2011. Responses were sought on years in practice; frequency of PBVD use; pre-operative allergy testing; and the number, severity and timing of anaphylactic reactions associated with PBVD use. A retrospective analysis was performed on survey responses. The full survey is appended to the article (see Supplementary Information Appendix S1).

Results

In total, 76 (42%) of members responded. One member who used methylene blue was excluded from the analysis. The remaining 75 members used PBVD on a median of 50 cases per year (0–250 cases per year) over a median of 10 years (4 months–15 years).

Incidence of anaphylaxis

Thirty-four members (45%) experienced what they considered to be definite anaphylactic reactions with PBVD such as blood pressure drop (15 members) or urticarial rash or hives (8 members). Seven members reported 'possible' anaphylaxis, with three of these members noting an urticarial rash and one member noted a drop in blood pressure. Although 33 members reported they did not experience anaphylactic reactions with PBVD use, 3 of these members reported skin rashes on their patients (Fig. 1).

Severity of anaphylaxis

Accounting for the varied responses, 44 members (58.7%) experienced some form of definite or possible allergic reaction to PBVD use. However, only 16 members (21%) experienced or witnessed severe anaphylaxis associated with a drop in blood pressure. Surgeons reported the most common reaction to PBVD was skin rash, followed by severe hypotension, although majority of surgeons did not experience any anaphylactic reactions from PBVD use (Fig. 2). There were no deaths from PBVD anaphylaxis reported by surgeons. Among the group, surgeons experienced or witnessed 78 cases of PBVD anaphylactic reactions of any severity in their total years of clinical practice. Fourteen surgeons (18.7%) reported experiencing at least two or more anaphylactic episodes during their practice (range: 0–10 cases). Based on the average number of cases with PBVD use per year by each surgeon over their total years of practice (51, 945 case-years), this gives an estimated overall reported incidence of anaphylactic reactions of any severity from PBVD use at 0.15%.

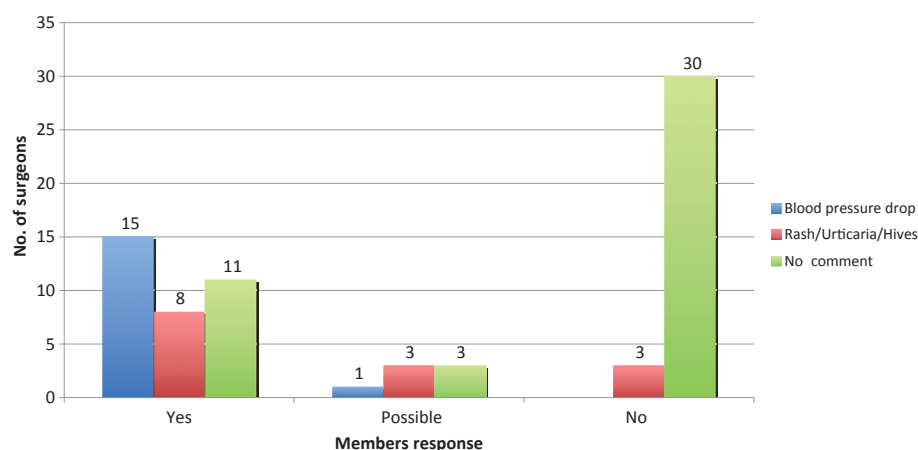


Fig. 1. Question: Have you had anaphylaxis associated with Patent Blue V dye use?

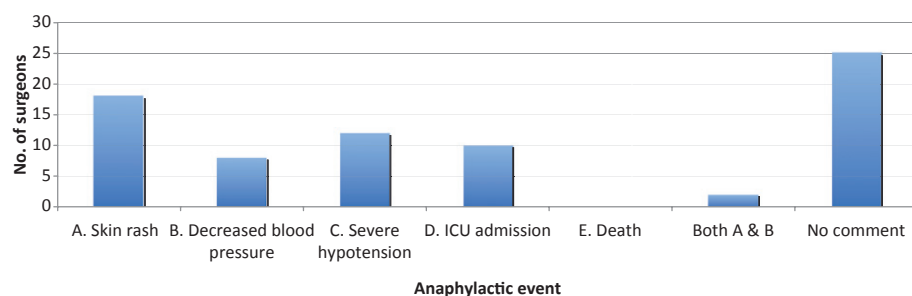


Fig. 2. Question: What was the worst anaphylaxis you have seen in response to Patent Blue V dye?

Post-anaphylaxis or preoperative skin allergy testing

Of the 34 members who reported what they considered definite anaphylaxis associated with PBVD use, only about half of these members (18 members, 52.9%) confirmed this with skin testing. Seven members (9.3%) reported routine preoperative skin testing for PBVD, while the remainder did not.

Timing of anaphylaxis

According to surgeons, the median time to developing manifestations of anaphylaxis after injection of PBVD was 20 min, but this could range from an immediate response to 90 min after surgery. Three members reported urticarial rashes on their patients only after the drapes were removed at the end of a 1-h operation without any changes to haemodynamic parameters.

Informed consent/attitude to PBVD ongoing use

Forty surgeons (53.3%) reported they would routinely include a discussion about the risk of PBVD allergy as part of their informed consent. Twenty-eight surgeons did not routinely have this discussion, eight members would only do so if patients asked for more details about their operation and one member would only include a discussion on PBVD allergy if there was a past history of allergy. Almost every surgeon (69 members, 90.8%) considered PBVD allergy as a predictable but rare event that the surgeon and anaesthetists should be aware of. Only a small proportion of surgeons consider PBVD allergy a misadventure (five members) or a misde-meanour (one member).

The majority of surgeons (58 members, 76.3%) agreed that 'the benefits of PBVD outweighed its anaphylactic risks', 5 members (6.6%) disagreed with that statement and 11 members (14.5%) were undecided (Fig. 3).

Discussion

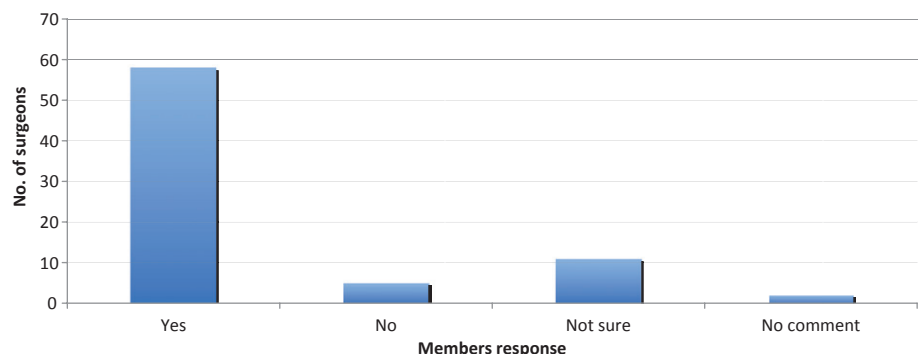
Omitting the use of PBVD could potentially lead to a lower sentinel node identification rate and this, in turn, could lead to an increased false-negative rate. A meta-analysis by Kim *et al.* demonstrated that the false-negative rate is affected by the SNB method used; being 10.9% for vital blue dyes alone, 8.8% for single agent radio-colloid and 7.0% when combined mapping modalities are used.¹² In the Italian Milan and GIVOM randomized clinical trials comparing

SNB to axillary dissection, the investigators used radioisotope alone and reported false-negative rates of 8.8% and 16.7% with negative predictive values of 95.4% and 92.3%, respectively.^{4,13} This compares to the Australasian SNAC trial where the majority of patients had a combination of mapping techniques reporting the sensitivity of sentinel node identification at 94.5%, false-negative rate at 5.5% and the negative predictive value of 98%.³ This survey has shown that majority of surgeons (76.3%) value the addition of PVBD in their clinical practices irrespective of the small but significant risk of anaphylaxis from its use.

Around the world, the commonly used blue dyes are PBVD (sodium Guerbet 2.5%) and its isomer isosulfan blue dye (ISBD, Lymphazurin 1%; Hirsch Industries Inc., Richmond, VA, USA). These are both triarylmethane dyes that share the same formula; however, PBVD has an additional hydroxyl group.^{14,15} PVBD is the most common blue dye used in surgical oncology in Australia and Europe. ISBD is the only vital dye that is approved by the Food and Drug Agency for use in SLN mapping in the USA.⁷ Reports of anaphylactic reactions related to PBVD and ISBD have percolated through the literature over the years.^{7,10,11,14–23} These allergic reactions are thought to be IgE-mediated with mast cell degranulation and histamine release,^{11,17,24} but delayed T-cell mediated reaction can also occur with reactions manifesting more than 1 h of administering PBVD.²⁴ In the survey, surgeons reported that a median time to anaphylaxis was approximately 20 min, but response could be immediate and up to 90 min after surgery. This is consistent with what is reported in the literature, with an average anaphylaxis time of 30 min, and ranging from an immediate anaphylaxis up to hours after the operation.^{7,11,16,18,19,24}

The prerequisite for an anaphylactic reaction is that the patient must be sensitized at the time of exposure, and thus, there is an IgE or occasionally IgG antibody-mediated reaction. IgE sensitization therefore is the result of prior exposure to either the agent causing the anaphylaxis or a substance sharing the allergenic epitopes with the agent.²⁰ PBVD is also used as a food colouring dye (E 131) in many countries, but it is not approved for use in Australia, New Zealand, Norway, Japan or the USA.^{15,25,26} PBVD and ISBD are structurally closely related to other triarylmethane dyes used in colour textiles, cosmetics, paper, leather, detergents, paints and inks. This type of prior exposure has been hypothesized to be responsible for the general population incidence of allergic sensitization when there has been no prior PBVD use.^{7,27} However, it is unknown what

Fig. 3. Question: Do the benefits of Patent Blue V dye outweigh the risk of significant allergic reaction?



the true incidence of community sensitization to PBVD is as there is the added complexity of regional variation of exposure to these dyes.¹⁰ Recent evidence suggests that the allergen to cause anaphylaxis may not be PBVD itself, but an unknown unique structure formed from the binding of a carrier to the PBVD hapten in the serum of the IgE-sensitized individual.²⁰ More research is required to investigate how PBVD causes its anaphylactic reactions.

Allergic reactions can be classified as grade 1 (urticaria, blue hives, pruritis or generalized rash), grade 2 (transient hypotension/bronchospasm/laryngospasm), grade 3 (severe hypotension requiring vasopressor support and/or high dependency unit/intensive care unit admission) and grade 4 (cardiorespiratory arrest and/or death).^{7,24,28} In this study, the severity of anaphylactic episodes encompassed almost all grades of allergic reactions except, fortunately, there were no deaths reported by these surgeons. Usually, in the absence of blue dye use in the perioperative setting, anaesthetic agents such as neuromuscular blocking drugs are the commonest cause of allergic reaction. Other causes include antibiotics, latex, colloids, opioids and local anaesthetic agents. The estimated incidence of anaphylaxis to anaesthesia and associated agents is 1/10 000–1/20 000 in Australia, with an estimated mortality of 5%.²⁸ The rate of neuromuscular blocking agent sensitization in the general population evaluated by the skin prick test is about 9.3%, but there is only a 1.4% risk of anaphylaxis occurring among previously sensitized subjects²⁸ which means not everyone with a positive skin test develops anaphylaxis on re-exposure to the agent. Similarly, Kalimo *et al.* reported that of 435 patients referred for lymphangiography, the skin prick testing (SPT) was positive in 2.8%.^{10,27} However, we know the actual risk of anaphylaxis from PBVD seen clinically is much lower. This has been shown for PBVD and ISBD with high levels of evidence derived from several large clinical trials and large case series. In the SNAC trial, 3 of 1088 (0.3%) randomized patients had an allergy to PBVD.³ The NSABP-32 trial⁵ reported allergic reactions to ISBD occurred in 0.7% of patients, but only 0.2% of them were grade 3 allergies; however, it is uncertain if post-operative skin allergy testing were performed. Montgomery *et al.* reviewed 2464 SLN mapping procedures performed at the Memorial Sloan–Kettering Cancer Center and reported an overall incidence of all allergic reactions to ISBD during SLN mapping at 1.6%, but only 0.4% of these were grade 3 reactions. However, again it is unclear whether confirmatory skin tests were performed in that study.⁷ The ACOSOG Z0010 trial reported a 0.1% incidence of anaphylaxis to ISBD in 4975 patients.²⁹ Barthelmes *et al.* reviewed a total of 7919 patients in the combined data from the ALMANAC trial and the UK-wide SNB training programme (NEW START) and showed 0.9% of patients experienced adverse reactions from PBVD use but only 5 patients (0.06%) experienced severe grade 3 allergic reactions.²⁴ Review by White *et al.* of all studies which published adverse reactions to vital blue dyes reported most studies in the literature documented the risk of anaphylactic reactions from PBVD or ISBD was in the order of $\leq 1\%$.^{8,17–19,21} The majority of these adverse reactions were easily manageable and that severe reactions are rare. White *et al.* reported the risk of severe anaphylaxis (grade 3) was as low as 0.06% and up to 0.4% when data were reviewed from large trials.⁸ The authors recommended that surgeons should continue to use vital dyes to ensure SNB remains a highly sensitive

procedure. Studies that published risks greater than 1% were often referring to all grades of anaphylaxis.^{8,16} The majority of these studies did not prove these anaphylactic reactions with confirmatory tests.^{5,7,17–19,21,22,29}

Our survey reported an overall incidence rate of 0.15% for any type of allergic reactions to PBVD; however, this is unlikely to be the true rate of allergic reactions or representative of all Australian and NZ breast surgeons' experiences due to the limitations of a retrospective survey study. Only 42% of members responded to the survey and most surgeons would have estimated the number of reactions from PBVD use in their experience. However, only about half of the surgeons in this survey performed skin allergy testing to confirm PBVD as the causative agent, which means these reactions may not be due to PBVD use alone. Despite these limitations, our conservative calculation is still consistent with what is currently reported in the literature.

Allergic reactions to drug agents can be tested by elevated serum tryptase levels, SPT and intradermal testing (IDT), with sensitivities of 54%, 80% and 100%.²⁴ SPT involves pricking the skin with a drop of the agent of interest on the patient's forearm. According to the European Society of Contact Dermatitis guideline for skin testing for adverse drug reactions,³⁰ a positive result from SPT is a wheal that is 3 mm greater than a negative control at 20 min with a delayed reading carried out 24 h later to exclude late reactions. It is advised the post-test holding time of a further 20 min (~20 min after completion of the test) be carried out to exclude the risk of a systemic reaction from the test, that is, the patient should remain under observation for 40 min after the commencement of the skin test.³¹ However, the presence of a positive SPT does not prove that the patient is clinically reactive to the allergen nor a negative test exclude the possibility of future allergy.^{28,31} IDT involves intradermal injection of 0.02–0.05 mL of the diluted solution to the surface of the arm to produce a wheal of more than 10 mm in diameter to indicate a positive result. If readings are negative at 30 min, subsequent IDT is performed with increasingly higher serial dilutions up to the pure solution at 30-min intervals as long as the test results of the previous dilution remain negative. Results are read again at 6 h, 24 h and 1 week after administration to exclude delayed reactivity. IDT could induce false-positive local and systemic reactions and should be done only if the SPT done under hospital surveillance³⁰ is negative. The utility of these cumbersome processes as a routine preoperative skin testing is not proven, and given the impracticality, it will probably never be tested.

According to the World Allergy Organization, currently there are no data available to confirm the predictive value of skin tests for anaphylactic reactions to drug allergies, so systematic screening of the general population is not recommended.²⁸ Although various bodies have advised using a test dose or SPT of vital blue dyes prior to full administration in the pre-operative setting,^{7,11,23} there is no evidence that this will reduce the incidence of anaphylaxis.^{27,28,30,32,33}

Provocation testing with allergen injection is not without its risks. A number of deaths have been reported from IDT but only one from SPT.^{31,34} It would be prudent for a patient undergoing SNB to be under a general anaesthetic and have the PBVD dye injected immediately after induction so there is a controlled airway if the patient does develop an anaphylactic reaction to PBVD.

Conclusion

The surgeons responding to this survey reported that the risk of anaphylaxis from PBVD is low. Although the surgeons were acutely aware of the possibility of anaphylaxis, the majority of the responders still use PBVD to assist with performing SNB. Performing routine preoperative SPT or IDT is impractical in elective surgeries and in any case is without a clear benefit. Patients should be informed about the small risk of allergy during the consent process and surgeons should inform anaesthetic colleagues when PBVD is used. The best situation for a patient during an episode of anaphylaxis is having a controlled airway under general anaesthetic. After an anaphylactic reaction, confirmatory testing should be carried out to ascertain the causative agent.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. BreastSurgANZ members survey on PBVD allergy.

Please note: Wiley-Blackwell is not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

Dear Colleague,

In response to the recent articles in the journal “Anaesthesia and Intensive Care “ (see attached) the executive of BreastSurgANZ requests you complete the following brief survey to provide an evidence base for a letter of response to the journal.

1. On average how many breast cancer (or other tumours) patients do you use Patent Blue V Dye (PBVD) each year?

Comment.....

2. How many years have you been using PBVD in your practice?

3. Have you had anaphylaxis associated with the use of PBVD?
 - a. Yes
 - b. No
 - c. Possible

Comment.....

4. Was it confirmed on allergy testing?
 - a. Yes
 - b. No

Comment.....

5. Do you routinely use preoperative allergy testing?
 - a. No
 - b. Yes
 - i. Skin testing
 - ii. Test dose in the operating theatre

Comment.....

6. How long after the injection did you get anaphylaxis?

Comment.....

7. What was the worst anaphylaxis you have seen in response to PBVD?
- a. Skin rash
 - b. Short term reduced blood pressure
 - c. Hypotension requiring full resuscitation
 - d. Hypotension requiring full resuscitation and ICU management with longer term consequences
 - e. Death

Number of times you have seen a severe reaction e.g. as described in c, d, or e.

Comments.....

8. Does your informed consent for all your patients include a discussion about the allergy issue with PBVD?
- a. Yes
 - b. No
 - c. If asked for small details
 - d. If history of allergy

Comments

9. Do you consider allergy to PBVD
- a. Misadventure
 - b. Misdemeanor
 - c. A predictable but rare event that the Surgeon and Anaesthetist should be aware of
10. Do the benefits of PBVD outweigh the risk of significant allergic reaction?
- a. Yes
 - b. No
 - c. Not sure

Comments.....

11. Other comments...

Thank you for your time. We will communicate the results to the membership and make a statement on the issue of PBVD Allergy on behalf of the society on our website.