

Original article

Anaphylaxis to patent blue V: a case series and proposed diagnostic protocol

Patent blue V is widely used in the identification of sentinel lymph nodes in patients with breast cancer and other malignancies. Individual case reports of allergy to patent blue V have been described in the medical literature since the 1960s. However, there is little data on clinical features and little experience of which allergy tests are appropriate or useful.

We gathered all cases of patent blue V allergy that had been seen and diagnosed in the Department of Allergy, Addenbrooke's Hospital over a 3-year period. We collected clinical details of each case including skin test results. For comparison we recruited 12 healthy control subjects who then underwent skin testing to patent blue V.

Six cases of patent blue V allergy were identified, all occurring during sentinel lymph node identification for breast carcinoma. All 6 had positive skin prick tests to neat patent blue V (25 mg/ml). Skin prick testing with a 1 : 10 dilution (2.5 mg/ml) produced positive results in 3 of 4 patients tested, and intradermal testing at a 1 : 100 dilution was (0.25 mg/ml) was positive in all patients tested. Of 12 control subjects, 11 had negative skin prick tests to both neat and 1 : 10 patent blue V with one subject showing a positive reaction to the higher concentration only.

On the basis of our experience of patent blue V allergy, we propose a diagnostic protocol that can be safely and reliably utilised in centres equipped for allergy testing.

**R. A. Haque, A. Wagner,
J. A. Whisken, S. M. Nasser,
P. W. Ewan**

Department of Allergy, Addenbrooke's Hospital,
Cambridge, UK

Key words: anaphylaxis; drug allergy; general
anaesthetic allergy; patent blue V.

Dr Rubaiyat Haque
Department of Allergy
Addenbrooke's Hospital
Cambridge
CB2 2QQ
UK

Accepted for publication 26 September 2009

Patent blue V is member of the triarylmethane group of synthetic dyes. It is also known as acid blue 3, disulphine blue and as the food additive E131 (1). In medical practice, patent blue V has traditionally been used to identify lymphatic vessels prior to cannulation for lymphography. More recently, the technique of sentinel lymph node biopsy has been developed as part of the staging procedure in patients with early breast cancer (2). The technique involves the subcutaneous injection of patent blue V into the affected breast. The dye is taken up by the lymphatic vessels and stains the sentinel lymph node blue allowing it to be identified and biopsied. Sentinel lymph node biopsy has been widely adopted for breast cancer management (3) and is also now being used in other malignancies including cutaneous melanoma (4) and cervical carcinoma (5).

The first reports of allergic reactions to patent blue V were published in the 1960s, mostly occurring in the context of lymphography (6, 7). There has since been a steady trickle of further case reports with almost all of the recent cases occurring during sentinel lymph node identification (8–20). As this technique gains popularity, the

numbers of reported cases of anaphylaxis are likely to increase further.

In this study, we present a case series comprising six patients referred to the Allergy Department at Addenbrooke's Hospital, Cambridge, UK for investigation of anaphylactic reactions that occurred during general anaesthesia. We describe the clinical features of reactions, our methods of investigation and diagnosis and propose a protocol for future investigation of suspected patent blue V allergy.

Case 1

This 66-year-old lady had several years earlier been diagnosed with carcinoma of the right breast that had been treated with a wide local excision. More recently, a suspicious lesion had been observed on mammography of the left breast. She was taken to theatre for further surgery and sentinel lymph node biopsy. At induction, she received midazolam, fentanyl, propofol, parecoxib and ondansetron. Ten minutes later, patent blue was

administered subcutaneously followed by a paravertebral block using bupivacaine. The sentinel node was identified and removed. Wide local excision of the breast lump commenced 25 min after the administration of patent blue at which point the patient's blood pressure dropped precipitously from a systolic pressure of 110–50 mmHg. This was accompanied by a sinus tachycardia of 120 beats per minute. Her tidal volume diminished, a wheeze was audible and blue-coloured peri-orbital angioedema observed. She was treated with intravenous boluses of 0.5–1.0 ml epinephrine 1 : 10 000, aminophylline 250 mg, hydrocortisone 500 mg, chlorphenamine 20 mg and a total of 4 l of intravenous fluids. She was transferred to the intensive care unit where she required an intravenous infusion of epinephrine. A tryptase level taken during the acute phase of the reaction was raised at 33.3 ng/ml (normal range 2–14 ng/ml) and then returned to a baseline level of 3.5 ng/ml. Skin prick testing (SPT) to patent blue V (25 mg/ml) was positive at both neat and 1 : 10 dilutions with weal sizes of 4 and 3 mm, respectively. Intradermal testing at a dilution of 1 : 100 also produced a positive reaction with an increase in weal diameter from 5 to 11 mm.

Case 2

This 69-year-old lady went to theatre for excision of a breast carcinoma and sentinel node biopsy. At induction, she received propofol, fentanyl, ondansetron and flucloxacillin. Shortly afterwards, she was given a subcutaneous injection of patent blue V. Thirty minutes later, she developed urticaria on her breasts, which then rapidly spread over her whole body. Her blood pressure dropped to 37/20 mmHg. Laryngoscopy showed slight oedema of the rima glottides but there was no evidence of bronchospasm. She was treated with intravenous epinephrine followed by chlorphenamine and dexamethasone. She made a rapid recovery, and her surgery was completed. She suffered erythema and angioedema of her arms and hands for several hours postoperatively but made an otherwise uneventful recovery. Tryptase levels were measured at 1, 3 and 24 h after the onset of the reaction. The results were 9.9, 21.1 and 7.6 ng/ml, respectively (normal range 2–14 ng/ml). SPT to patent blue V (25 mg/ml) showed a 5 mm positive reaction. Intradermal testing at a dilution of 1 : 100 also gave a positive reaction with an increase in weal size from 5 to 14 mm, confirming the diagnosis of patent blue V allergy.

Case 3

This 42-year-old lady underwent a wide local excision for carcinoma of the left breast with sentinel lymph node biopsy. Induction was with propofol and fentanyl. Twelve minutes later, patent blue V was injected around

the left nipple. Eight minutes after this she received an intravenous infusion of diclofenac. Five minutes later, she developed a marked tachycardia, a fall in blood pressure from 110/60 mmHg to 60/30 mmHg and generalized erythema. The operation was abandoned, and she was transferred to the intensive care unit for further treatment. Serum tryptase levels taken at 3, 6 and 24 h after the reaction were all within the normal range at 8, 9 and 3 ng/ml, respectively. SPT to patent blue V (25 mg/ml) at a dilution of 1 : 10 was negative but a small 3 mm positive reaction (with a 16 mm flare) was observed with the undiluted solution. Intradermal testing with a 1 : 100 dilution showed a strong positive reaction with an increase in weal diameter from 6 mm to 12 mm.

Case 4

This 56-year-old lady required excision of a breast lump with sentinel node biopsy. She received midazolam and fentanyl followed several minutes later by propofol and then morphine. Patent blue V was then injected, and 15 min later, she developed hypotension, generalized erythema and severe facial angioedema. There was no respiratory compromise. The reaction was protracted, and she required an epinephrine infusion for approximately 24 h postanaesthetic. A serum tryptase level taken acutely was raised at 133 ng/ml and had dropped to 28.5 ng/ml after 24 h. The baseline tryptase was normal at 6.0 ng/ml. SPT to patent blue V (25 mg/ml) at 1 : 1 and 1 : 10 dilutions were positive (weal diameters of 5 mm and 3 mm respectively), and intradermal testing was not carried out.

Case 5

This 46-year-old lady with an invasive ductal carcinoma of the right breast underwent a mastectomy with sentinel lymph node biopsy. She received midazolam, propofol and atracurium at induction followed by ceftriaxone. Approximately 30 min after the injection of patent blue V, her oxygen saturation dropped to 89% as did her blood pressure to 55/25 mmHg. There was no urticaria or angioedema. She was treated successfully with ephedrine, hydrocortisone and chlorphenamine, and the operation was completed. Serum tryptase rose acutely to 105 ng/ml and returned to a baseline of 4.7 ng/ml. SPT to neat patent blue V (25 mg/ml) gave a 5 mm positive reaction as did intradermal testing at a 1 : 100 dilution (increase in weal size from 5 to 14 mm).

Case 6

This 70-year-old lady underwent breast lump excision and sentinel lymph node identification. Patent blue V was

Table 1. Clinical characteristics and clinical features of allergic reactions to patent blue V in all six patients

Case	Age	Time to onset of reaction (min)	Hypotension	Bronchoconstriction	Urticaria/erythema	Angioedema	Maximum tryptase level (ng/ml)	Baseline-tryptase level (ng/ml)
1	66	25	X	X		X	33.3	3.5
2	69	30	X		X	X	21.1	7.6
3	42	13	X		X		9	3
4	56	15	X		X	X	133	6
5	46	30	X	X			105	4.7
6	70	55	X	X		X	ND	3.5

Table 2. Skin prick test (SPT) and intradermal test results in all six patients

Case	SPT patent blue V 1 : 1 (25 mg/ml)		SPT patent blue V 1 : 10 (2.5 mg/ml)		SPT patent blue V 1 : 100 (0.25 mg/ml)		
	Weal diameter (mm)	Flare diameter (mm)	Weal diameter (mm)	Flare diameter (mm)	Initial Weal diameter (mm)	Final Weal diameter (mm)	Flare diameter (mm)
1	4	NR	3	NR	5	11	18
2	5	NR	ND	ND	5	14	NR
3	3	16	0	0	6	12	35
4	5	25	3	0	ND	ND	ND
5	6	NR	ND	ND	5	14	> 30
6	5	10	5	12	4	10	20

ND, not done; NR, result not recorded in case notes.

administered 15 min before induction of anaesthesia with fentanyl and propofol followed by intravenous paracetamol and morphine. Approximately 40 min after induction, she developed hypotension with the systolic pressure falling to 40 mmHg and a drop in oxygen saturation to 78%. She developed gross angioedema affecting her face and hands and required ventilation for 36 h postoperatively. SPT was positive to patent blue V (25 mg/ml) at both 1 : 1 and 1 : 10 dilutions with weal diameters of 5 mm for both. Intradermal tests also showed a clear positive reaction with an increase in weal size from 4 mm to 10 mm.

A summary of the clinical characteristics of each patient's reaction including tryptase level is shown in Table 1. Table 2 summarizes the SPT and intradermal test results in each case. To determine whether the positive SPT and intradermal test results were as a result of hypersensitivity to patent blue V rather than a nonspecific irritant reaction, we recruited 12 healthy control subjects who had no history of anaphylaxis to general anaesthetic agents or to patent blue V. Eleven of the 12 control subjects had negative SPT to patent blue V at both 1 : 1 and 1 : 10 dilutions. One control subject, however, did have a small positive SPT (4 mm weal and 20 mm flare) to 1 : 1 patent blue V but with a negative reaction at a 1 : 10 dilution. An intradermal test was performed in this subject at a dilution of 1 : 100 and was borderline positive with no expansion of weal diameter but with a 25 mm flare. This subject had no previous history of known exposure to patent blue V. She did not report a history of adverse reactions to blue food colourings.

Discussion

Hypersensitivity reactions to subcutaneous injections of patent blue V are now well recognized but the reported prevalence of this allergy varies greatly. Kalimo in 1981 (21) reported six cases of anaphylaxis in a series of 273 patients who had undergone lymphography with patent blue V, giving a frequency of 2.2%. Five of these cases had a positive SPT result to patent blue V and one a negative SPT but positive intradermal test. In a more recent series of 371 patients in whom sentinel lymph node identification was performed, four suffered allergic reactions that were attributable to patent blue V injection: a frequency of 1.1% (16). The lowest frequency of allergic reactions was reported by Mansouri in 2006. Sentinel node biopsy using patent blue V in 416 patients with breast carcinoma led to only one allergic reaction (0.24%) (22). Finally, Keller reported 3 cases of patent blue V allergy amongst an estimated number of 370 sentinel node biopsies (0.8%) (18).

All 6 of our cases has positive skin tests to patent blue V (SPT or intradermal), the onset of the clinical reaction was relatively quick, between 13 and 55 min after subcutaneous injection, and mast cell tryptase levels after the reaction were raised in four of the five patients in whom this was measured (Table 1). All of this adds to the likelihood that these reactions are mediated by a type 1 hypersensitivity. Further evidence of the IgE-mediated nature of these reactions is supplied by Wöhrle et al. (13) who demonstrated the presence of specific IgE to patent blue V (as well as to isosulfan blue with which patent blue strongly cross-reacts) with an enzyme-linked immunosor-

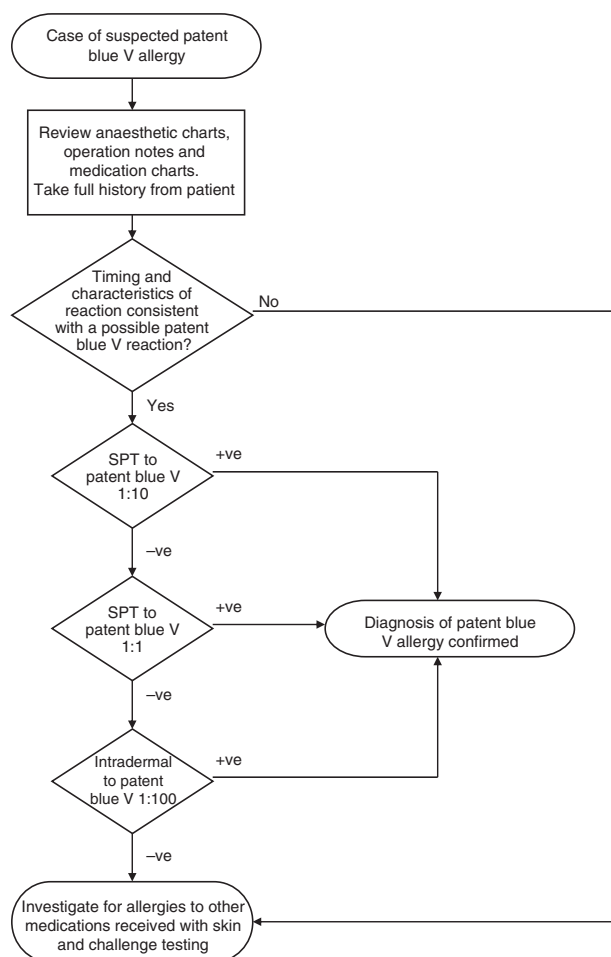


Figure 1. Proposed protocol for investigation of suspected allergic reactions to patent blue V. SPT at a 1 : 10 dilution can be omitted. A proportion of allergic patients can be picked up with this test alone, avoiding the need for exposure to a higher concentration of patent blue V, but there were no systemic adverse reactions to the 1 : 1 solution.

bent assay (ELISA). A negative lymphocyte stimulation test in another case of patent blue V anaphylaxis supports the notion that the reaction is not T-cell-mediated (18). Patent blue V is used in the textile, agriculture and paper industries as well as being present in certain cosmetics, medicines and foods. Sensitisation is therefore possible through exposure to any of these products.

Recently, Mertes et al. (20) published the largest series so far of 14 patients who had suffered allergic reactions patent blue V. The clinical symptoms, time from injection to onset of reactions and overall severity of reactions were broadly similar those cases presented here. SPT was positive in eight patients and negative in five but intradermal tests were positive in all of their patients. The Mertes et al. study recommends intradermal testing in patients who are SPT negative for patent blue V, adding further weight to our proposed diagnostic protocol (Fig. 1), which includes this recommendation.

In the light of the consistent skin test positivity to patent blue V in all of our cases, one might propose prospective skin testing in all patients undergoing sentinel lymph node biopsy. However, this would be an impractical proposition. The frequency of anaphylaxis to patent blue V is sufficiently low for routine prospective skin testing to be unnecessary. Also, the false positive rate of SPT to patent blue V is unknown. In our small control group, we observed one positive skin test, the significance of which has not yet been determined. This positive skin test result in one control subject can be interpreted in one of three ways: (i) the subject is allergic to patent blue V, (ii) the patient has been sensitized to patent blue V but is not allergic or (iii) this is a false positive result caused by a nonspecific irritant response. Without performing further challenge testing, it is not possible to determine, which of these is the correct interpretation.

It is also important to note that without knowledge of false positive rates of skin tests to patent blue V, one must always keep in mind the possibility that other drugs given during the procedure (muscle relaxants, general anaesthetic agents, antibiotics and nonsteroidal anti-inflammatory drugs) may have caused the reaction. Therefore, appropriate testing (SPT, intradermal tests and challenge tests if necessary) for all other suspected drugs that the patient has received should be carried out if clinical suspicion is sufficiently high. All cases presented in this study underwent investigation for all additional drugs received at the time of the procedure.

One might also consider the use of alternative dyes to patent blue V to avoid the problem of anaphylaxis. Isosulfan blue and methylene blue are two such alternatives. Isosulfan blue has a strong structural homology and cross-reactivity with patent blue V so is unlikely to be a useful alternative. The frequency of allergic reactions with isosulfan blue is of a similar order to that of patent blue (0.8–1.9%) (23, 24). Methylene blue, on the other hand, rarely induces anaphylaxis [although it has been reported (25)] but has the disadvantage of inducing skin necrosis and ulceration (26, 27).

Finally, based on our experience with patent blue V anaphylaxis, we propose a scheme for the systematic diagnosis of such cases (Fig. 1) that requires prospective validation. We would recommend that such testing is carried out in a centre with experience in the diagnosis of drug allergies including general anaesthetic allergies.

In summary, patent blue V has an important role in sentinel lymph node identification and biopsy, and its use in the surgical management of cancer patients is growing. This increased usage has led to greater numbers of allergic reactions, bringing it to the attention of allergy specialists. The incidence of this allergy is small, and screening for it prior to patent blue V injection is unnecessary. The descriptions of the clinical features published here along with the proposed protocol for investigation should assist specialists in accurately and safely diagnosing patent blue V allergy in the future.

References

1. Scherer K, Bircher AJ, Figueiredo V. Blue dyes in medicine—a confusing terminology. *Contact Derm* 2006;**54**:231–232.
2. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg* 1994;**220**:391–398.
3. Krag D, Weaver D, Ashikaga T, Moffat F, Klimberg VS, Shriver C et al. The sentinel node in breast cancer—a multi-center validation study. *N Engl J Med* 1998;**339**:941–946.
4. Morton DL, Wen DR, Wong JH, Economou JS, Cagle LA, Storm FK et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992;**127**:392–399.
5. Barranger E, Grahek D, Cortez A, Talbot JN, Uzan S, Darai E. Laparoscopic sentinel lymph node procedure using a combination of patent blue and radioisotope in women with cervical carcinoma. *Cancer* 2003;**97**:3003–3009.
6. Kopp WL. Anaphylaxis from alphanazurine 2G during lymphography. *JAMA* 1966;**198**:668–669.
7. Sinclair DJ, Perera FA. Allergic reactions: following patent blue dye injection. *Can Med Assoc J* 1969;**101**:100–101.
8. Woltsche-Kahr I, Komericki P, Kranke B, Brabek E, Horn M, Schuller-Petrovic S et al. Anaphylactic shock following peritumoral injection of patent blue in sentinel lymph node biopsy procedure. *Eur J Surg Oncol* 2000;**26**:313–314.
9. Mullan MH, Deacock SJ, Quiney NF, Kissin MW. Anaphylaxis to patent blue dye during sentinel lymph node biopsy for breast cancer. *Eur J Surg Oncol* 2001;**27**:218–219.
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. Ingram D, Hewett L, Maddern P. Anaphylaxis to patent blue during sentinel lymph node biopsy. *ANZ J Surg* 2004;**74**:607–608.
12. Bouman EA, Songun I, Marcus MA. A case of an anaphylactic reaction to an old substance—patent blue—for a new indication. *Acta Anaesthesiol Scand* 2004;**48**:1066.
13. Wohrl S, Focke M, Hinterhuber G, Stingl G, Binder M. Near-fatal anaphylaxis to patent blue V. *Br J Dermatol* 2004;**150**:1037–1038.
14. Olsha O, Carmon M. Blue hives localized to the opposite arm after patent blue v injection for lymph node mapping in breast cancer. *Breast J* 2005;**11**:468.
15. van ZE, Polderman MC, Kuijken I. Anaphylaxis to patent blue during sentinel lymph node identification. *Contact Derm* 2005;**53**:171.
16. Beenen E, de Roy van Zuidewijn DB. Patients blue on patent blue: an adverse reaction during four sentinel node procedures. *Surg Oncol* 2005;**14**:151–154.
17. Dewachter P, Mouton-Faivre C, Benhaijoub A, bel-Decollogne F, Mertes PM. Anaphylactic reaction to patent blue V after sentinel lymph node biopsy. *Acta Anaesthesiol Scand* 2006;**50**:245–247.
18. Keller B, Yawalkar N, Pichler C, Braathen LR, Hunger RE. Hypersensitivity reaction against patent blue during sentinel lymph node removal in three melanoma patients. *Am J Surg* 2007;**193**:122–124.
19. Weng PW, Hsu HM, Chen TW, Hsieh CB, Chang TM, Chen VT et al. Blue angioedema of eyelid after patent blue injection for lymphatic mapping procedure. *Eur J Cancer Care (Engl)* 2007;**16**:390–391.
20. Mertes PM, Malinovsky JM, Mouton-Faivre C, Bonnet-Boyer MC, Benhaijoub A, Lavaud F et al. Anaphylaxis to dyes during the perioperative period: reports of 14 clinical cases. *J Allergy Clin Immunol* 2008;**122**:348–352.
21. Kalimo K, Jansen CT, Korman M. Sensitivity to Patent Blue dye during skin-prick testing and lymphography. A retrospective and prospective study. *Radiology* 1981;**141**:365–367.
22. Mansouri R, Chicken DW, Keshtgar MR. Allergic reactions to patent blue dye. *Surg Oncol* 2006;**15**:58.
23. Leong SP, Donegan E, Heffernon W, Dean S, Katz JA. Adverse reactions to isosulfan blue during selective sentinel lymph node dissection in melanoma. *Ann Surg Oncol* 2000;**7**:361–366.
24. Cimmino VM, Brown AC, Szocik JF, Pass HA, Moline S, De SK et al. Allergic reactions to isosulfan blue during sentinel node biopsy—a common event. *Surgery* 2001;**130**:439–442.
25. Dewachter P, Mouton-Faivre C, Trechot P, Lleu JC, Mertes PM. Severe anaphylactic shock with methylene blue instillation. *Anesth Analg* 2005;**101**:149–50, table.
26. Salhab M, Al SW, Mokbel K. Skin and fat necrosis of the breast following methylene blue dye injection for sentinel node biopsy in a patient with breast cancer. *Int Semin Surg Oncol* 2005;**2**:26.
27. Stradling B, Aranha G, Gabram S. Adverse skin lesions after methylene blue injections for sentinel lymph node localization. *Am J Surg* 2002;**184**:350–352.