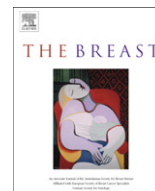




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Original article

Investigation of anaphylactic reaction after patent blue V dye injection

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ABSTRACT

Background: Patent blue dye V (PBV) is in widespread use for sentinel node biopsy in breast cancer and melanoma. At present, the best diagnostic approach in investigating possible anaphylaxis due to PBV is not defined.

Method: We reviewed our experience of patients and the cases reported in the literature that developed an anaphylactic reaction after injection of PBV and suggest a diagnostic protocol. From May 2006 to April 2009 six patients were known to the Cardiff anaesthetics department to have suffered a severe anaphylactic reaction after injection of PBV. We amalgamated the results of the investigations of our patients with those of 42 case reports published in the literature during the last 10 years.

Results: Of 40 patients with a documented allergy history 31 patients did not have a past medical history of allergy. The median interval between PBV administration and allergic reaction was 15 min (range 1 min–180 min). Of 20 patients with hypotension 18 received inotropes. 4 patients had a fall in blood pressure as their sole symptom. 23 patients had urticaria or other allergic skin manifestations, 8 had blue wheals. 5 patients had bronchospasm. 2 patients had a cardiac arrest. They were successfully resuscitated. The median dose of PBV was 2 ml (range 0.5 ml–5 ml). Tryptase levels were elevated in 14 of 26 tested patients. Skin prick testing was positive in 24 of 30 tested patients. Intradermal testing was positive in all 13 tested patients.

Conclusion: Most patients experiencing a severe allergic reaction to PBV have no past medical history of allergy. The value of formal allergy skin testing for PBV-related allergy lies in excluding other agents as the causative factor to avoid their exposure in the future.

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Background

Patent blue dye V (PBV) is in widespread use for sentinel node biopsy in breast cancer and melanoma. 0.56% patients develop allergic reactions, 0.06% of patients develop severe anaphylaxis.¹ At present, the best diagnostic approach in investigating possible anaphylaxis due to PBV is not defined. We reviewed our experience of patients and the cases reported in the literature that developed an anaphylactic reaction after injection of PBV and suggest a diagnostic protocol.

Patients and methods

From May 2006 to April 2009 six patients were known to the Cardiff anaesthetics department to have suffered a severe anaphylactic reaction after injection of PBV. This included four

patients referred to allgergo-anaesthetic outpatients from elsewhere as well as two patients admitted to the local high dependency unit. We amalgamated the results of the investigations of our patients with those reported in the literature. Cases from the literature were identified by searching MEDLINE and EMBASE since 1999 including the non-English literature combining the medical subject headings (MeSH) sentinel node biopsy, hypersensitivity, patent blue V and hand-searching the references. Adverse reactions to isosulphan blue, an isomer of PBV, were excluded as it is not available in Europe and its incidence of allergies is slightly higher.¹ Analysing our cases and those reported in the literature (see Table 1) we recorded the dose of PBV to detect a potential relationship between dose and severity of the allergic reaction. We took note of the presence or absence of a past medical history of allergy or atopia to test the hypothesis whether a history of allergy is a marker of increased risk of anaphylaxis to PBV. We recorded the interval between PBV injection and the event and the presenting symptoms. We documented use of vasopressors, referral to HDU or a change/abandoning of the procedure which are the characteristics of a severe anaphylactic reaction as previously classified.¹ Regarding

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Table 1
Reported cases.

Author	Onset	Symptoms	Treatment				Dose	Allergy history	Tryptase	Skin prick test	Intra-dermal-test	Other
			Vaso-pressor	ICU	ventilation	Procedure changed/abandoned						
Barthelmes L 2010	15 min	Hypotension Bronchospasm	✓	✓	✓		2 ml	No	↑	PBV		
	In recovery	Hypotension Rash					2 ml	No	Not tested	PBV Morphine		
	15 min	Hypotension Laryngeal oedema Rash	✓	✓	✓		2 ml	No	↑	+ve		
	5 min	Hypotension Angiooedema Rash					2 ml	No	↑	+ve		
Sleth JC 2008 ³	40 min	Hypotension Blue wheals	✓	✓	✓		2 ml	No	↑			
	40 min	Blue wheals Masseter spasm	✓	✓	✓		2 ml	Nickel				
	15 min	Hypotension	✓				2 ml	No		+ve		-ve SPT methylene blue
Mertes PM 2008 ⁴	30 +/- 6 min (10–60)	Hypotension 11/14 Bronchospasm 1/14 Urticaria 11/14	11/14	9/14				5/14	3/9	9/14	11/11	
Lanitis S 2008 ⁵	10 min	Hypotension	✓				4 ml	Not recorded	↑	+ve		Weakly + ve SPT to ondasetron
Thierrin L 2008 ⁶	180 min	Cardiac arrest	✓	✓	✓		2 ml	No	N	Omitted because of high risk of anaphylaxis due to testing		-ve SPT to all other anaesthetic agents
Keller B 2007 ⁷	30 min	Urticaria Hypotension					4 ml	Not recorded		+ve		Unrecognised allergic reaction to PBV at first exposure. At 2nd exposure similar reaction.
	10 min	Urticaria	✓				4 ml	Not recorded				
Hadar T 20 06 ⁸	–						Not recorded	No		-ve	+ve	
Dewachter P 2006 ⁹	45 min	Urticaria Hypotension	✓				Not recorded	Noramidopyrine				
van Zuuren E 2005 ¹⁰	15 min	Hypotension Angiooedema	✓				5 ml	Not recorded		+ve		WLE + SNB followed by completion mastectomy + ANC presumed sensitisation at first operation
Beenen E 2005 ¹¹	–	Blue hives					2 ml	No				
	–	Blue hives					2 ml	No				
	–	Blue hives					2 ml	No				
Olsha O 2005 ¹²	5 min	Hypotension				✓	2 ml	No				
	75 min	Blue hives					2 ml	Not recorded				
Noirot A 2005 ¹³	15 min	Hypotension		✓		✓	2 ml	No	↑	+ve		
Wohrl S 2004 ¹⁴	10 min	Cardiac arrest - CPR	✓			✓	0.5 ml	No		+ve	+ve	
Bouman EAC 2004 ¹⁵	20 min	Hypotension Bronchospasm Urticaria					Not recorded	Atopia	↑			
Galatius H 2003 ¹⁶	30 min	Hypotension Urticaria	✓	✓	✓		0.5 ml	No				
	30 min	Urticaria	✓			✓	0.75 ml	No				
	5 min	Urticaria Hypotension Bronchospasm	✓	✓			0.75 ml	No				
Forschner K 2003 ¹⁷	5 min	Hypotension Urticaria	✓				1 ml	No	↔	+ve		
Crivellaro M 2003 ¹⁸	10 min	Hypotension Urticaria	✓				1 ml	no	↑	-ve	+ve	
Vrancken Peeters MJTDF 2000 ¹⁹	15 min	Bronchospasm		✓		✓	1 ml	Zink oxide tape		+ve		
Mullen MH 2001 ²⁰	Patient A 15 min	Hypotension Erythematous rash	✓	✓		✓	2 ml	Not recorded		+ve		
van der Horst J C 2001 ²¹	Patient B 1 min	Blue wheals Hypotension Bronchospasm	✓	✓	✓	✓	0.5 ml	Not recorded		+ve		+ve SPT to muscle relaxants + morphine
	1 min	Urticaria				✓	0.6 ml	No		+ve		First op abandoned re-scheduled + re-exposure 1 week later → urticaria
Woltsche-Kahr I 2000 ²²	1 min	Lip swelling						No		-ve	+ve	
Salvat J 1999 ²³	20 min	Blue wheals Hypotension		✓			4 ml	No	Not done			

investigation of the adverse event we recorded the results of tryptase levels and skin testing. Elevated serum tryptase levels are encountered following an acute allergic episode. Skin-prick and intradermal testing allows further determination of the causative allergen. In skin-prick testing a drop of the putative allergen is placed on the volar surface of the forearm. The skin is pricked through the drop with a lancet. A positive result is defined as a wheal that is 3 mm greater than that made by the negative control (0.5% phenol in 0.9% saline) or half the size of the positive control (histamine hydrochloride - 10 mg mL⁻¹). Intradermal testing involves intradermal injection of 0.02–0.05 ml of dilute solution. If after 30 min the result is negative further injections are performed with increasingly higher serial dilutions up to the pure solution.²

Results

We identified 48 patients in 22 publications of allergy due to PBV in the last 10 years including our own (see Table 1). Results of the combined analysis of the published cases and our own are shown in Table 2.

Of 40 patients with a documented allergy history 31 patients did not have a past medical history of allergy. 9 patients reported a history of atopia or allergic reactions to various allergens (nickel, normidopyrine, zink oxide tape), none of which related to PBV.

The median interval between PBV administration and allergic reaction was 15 min (range 1 min–180 min).

Of 20 patients with hypotension 18 received inotropes. 4 patients had a fall in blood pressure as their sole symptom. 23 patients had urticaria or other allergic skin manifestations, 8 had blue wheals. 5 patients had bronchospasm. 2 patients had a cardiac arrest. They were successfully resuscitated and recovered without any further sequelae.

The median dose of PBV was 2 ml (range 0.5 ml–5 ml). There was no relationship between PBV dose and severity of the allergic reaction ($p = 0.655$, Yates' $\chi^2 = 2.441$). Even the minimum dose of 0.5 ml lead to a dramatic reaction and cardiac arrest in one patient.¹⁴ Tryptase levels were elevated in 14 of 26 tested patients. Skin prick testing was positive in 24 of 30 tested patients. Intradermal testing was positive in all 13 tested patients including 6 patients in whom skin prick testing was negative. Sensitivity of tryptase, skin prick and intradermal testing was 54 %, 80 % and 100 %, respectively (Table 3).

Table 2
Presentation, management and investigation of PBV-associated allergy.

	Current series	Literature	Total
Allergy history	1/6	8/34 ^a	9/40
Onset of allergy	15 min (5–40 min)	15 min (1–180 min)	15 min (1–180 min)
Symptoms/signs			
Urticaria/wheals/rash	4/6	30/42	23/48 (48%)
Hypotension	4/6	16/42	20/48 (42%)
Bronchospasm	1/6	4/42	5/48 (10%)
Inotrope use	4/6	14/42	18/48 (38%)
ICU/HDU admission	5/6	8/42	13/48 (27%)
Cardiac arrest	—	2/42	2/48 (4%)
Abandoning/change of procedure	—	8/42	8/48 (17%)
Investigations			
↑ tryptase	5/5	9/21	14/26
+ve SPT ^b	4/4	20/26	24/30
+ve intradermal testing	—	13/13	13/13
Dose	2 ml	2 ml (0.5–5 ml)	2 ml (0.5–5 ml)

^a 8 patients – allergy history not recorded.

^b SPT – skin prick test.

Table 3
Investigation of PBV-associated allergy.

Test	Sensitivity
Tryptase	14/26 (54%)
Skin prick test	24/30 (80%)
Intradermal testing	13/13 (100%)

Discussion

The allergic potential of PBV has long been recognised.²⁴ Its increasing use for sentinel node biopsy lead to publication of 48 cases experiencing an allergic reaction to PBV during the last 10 years. We prospectively recorded 44 (0.56%) allergic reactions including 5 (0.06%) severe reactions in 7917 sentinel node biopsies in the ALMANAC trial and NEW START training programme¹ which proves it to be a much more potent allergen compared to other agents incriminated of perioperative anaphylaxis such as muscle relaxants – 1:6500 (0.0002%) muscle-relaxant containing anaesthetics²⁵ – and even less frequently latex and antibiotics. 31 of 40 patients (78%) did not have a past medical history of allergy. 2 patients who experienced an (unrecognised) allergic reaction at previous intraoperative PBV exposure experienced a similar reaction when re-exposed to PBV.^{7,22} Taking an allergy history should form part of the assessment of any patient prior to surgery, but the absence of an allergy does not reduce the risk to allergy to PBV. There are no reports of adverse reactions to PBV in patients with a food allergy or an allergy to E 121. Therefore, selective pre-operative skin testing of patients with a known allergic predisposition or food allergy does not appear to be beneficial and justifiable.

Tryptase was elevated in 14 of 26 tested patients (sensitivity 54% - Table 3). Elevated tryptase levels at the time of the event are suggestive of anaphylaxis due to mast cell activation²⁶. Its positive and negative predictive value in the diagnosis of anaphylaxis during anaesthesia is 93% and 54%, respectively.²⁷ Normal tryptase levels do not exclude an allergic mechanism of the reaction.²⁸ Some allergic reactions are mediated by basophil and complement activation that do not trigger a rise in tryptase levels. Intravenous fluid replacement used for resuscitation and correction of hypotension may dilute and lower serum tryptase levels²⁹.

Skin prick testing was positive in 24 of 30 tested patients (sensitivity 80% - Table 3). 6 patients whose skin prick test was negative tested positive on intradermal testing. Despite better sensitivity intradermal testing should be reserved for patients whose skin prick test was negative due to the increased risk of severe allergic reactions because of intradermal testing itself.³⁰

The underlying mechanism of an allergy to PBV remains unclear. Some favour a classical IgE immune complex driven mechanism¹⁷. Wohrl detected PBV and isosulfan blue specific IgE in a patient with near-fatal anaphylaxis to PBV using ELISA (enzyme-linked immunosorbent assay)¹⁴. Widespread sensitisation to PBV could occur due to its common use as a food additive (E 131) and in textiles. However, in the presence of preformed antibodies injection of PBV should lead to an immediate immune response. Immediate anaphylaxis is uncommon²². Most reactions occur delayed (median 15 min) supporting a non-immune complex mediated process of mast cell activation. Nonetheless, 2 patients experienced a severe reaction within 1 min of administering PBV and in three further patients it happened within 5 min. Should a severe allergic reaction manifest itself early after injection of PBV it may be safest to abandon or shorten the intended procedure as reported in 8 patients. Preoperative prophylaxis has shown to reduce the severity of the allergic reactions, which is also considered suggestive of a non-IgE mediated immune response.³¹

The value of allergy testing after an event involving PBV is to exclude potential allergens other than PBV, exposure of which is to

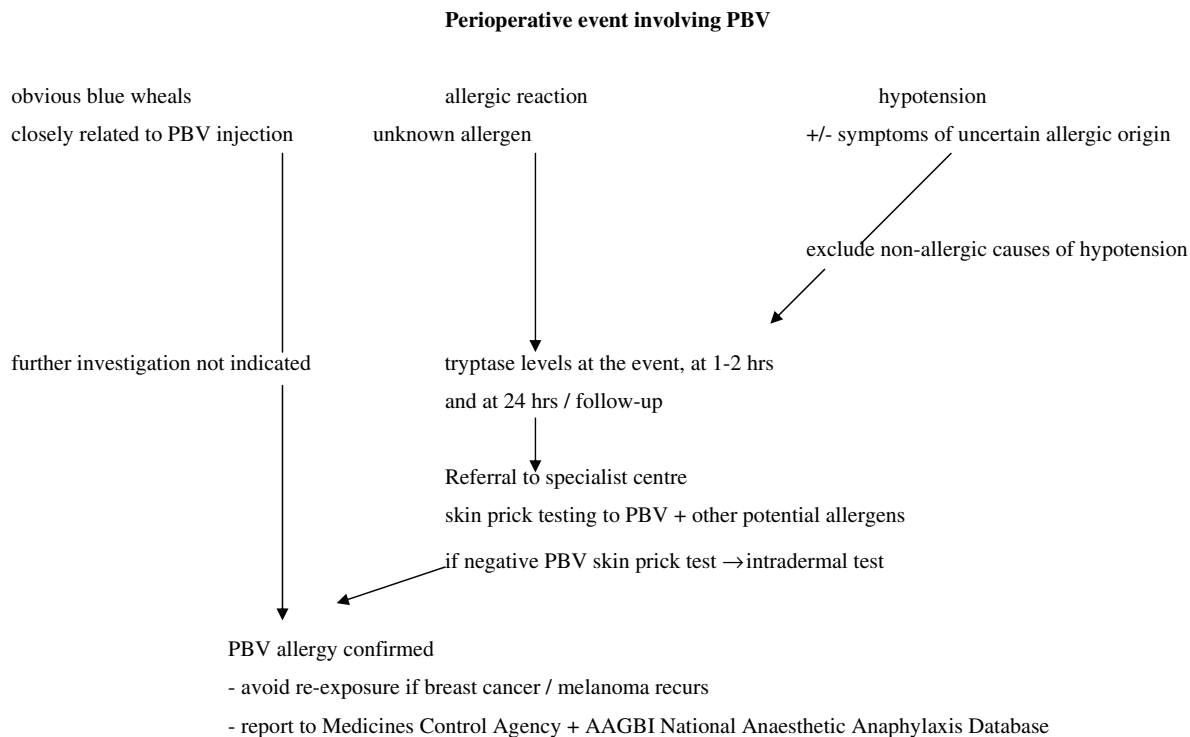


Fig. 1. Perioperative event involving PBV.

be avoided in the future. Obvious blue wheals following PBV injection are diagnostic of PBV allergy. Further diagnostic work-up has no implications for the patient and can be omitted, as most patients require injection of PBV only once in their lifetime.

Patients who develop hypotension only without other symptoms of anaphylaxis and patients who develop skin changes of uncertain allergic etiology warrant detailed investigation. For these patients it is important to exclude non-allergic reasons of hypotension and investigate other potential allergens as this could have implications for future anaesthetics. Elevated tryptase levels at the time of the event confirm the allergic nature of the episode, normal levels do not exclude them²⁶.

Pre-operative allergy skin testing has been shown to reduce the rate of allergic reactions to 0.5% patients (2 of 435 patients) when PBV was only administered to patients who tested negative to PBV compared with 2.2% (6 of 273 patients) to all comers without prior testing ($p = 0.05$).³² We consider this approach impractical given the relatively low number of severe allergic reactions compared to the high volume of breast cancer patients undergoing sentinel node biopsy. Selective skin allergy testing may be advantageous in the few patients who develop a recurrence of their breast cancer or malignant melanoma to exclude sensitisation at their initial cancer treatment. Alternatively, PBV could be omitted accepting a 4% risk of missing further involved sentinel nodes using the single injection technique of nanocolloid only.³³

A possible diagnostic protocol for PBV associated allergic reactions in line with recommendations by the Association of Anaesthetists of Great Britain and Ireland³⁴ is suggested below (Fig. 1).

Skin testing at a specialist centre aims at identifying the likely allergen. Cases of confirmed PBV allergy should be reported to the Medicines Control Agency (<http://yellowcard.mhra.gov.uk/>) and the AAGBI National Anaesthetic Anaphylaxis Database (http://79.123.101.84/fmi/iwp/cgi?-db=AAGBI_NAA_Database&-loadframes) Tables 2 and 3.

Summary

Most patients experiencing a severe allergic reaction to PBV have no past medical history of allergy. The exact mechanism of PBV-related anaphylaxis remains unknown. The value of formal allergy skin testing for PBV-related allergy lies in excluding other agents as the causative factor to avoid their exposure in the future.

Conflict of Interest Statement

None declared.

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