Original article

Anaphylaxis to dyes during the perioperative period: Reports of 14 clinical cases

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Background: Vital dyes are widely used for lymphatic mapping and sentinel lymph node biopsy in patients with malignant tumors, and reports of anaphylactic reactions are becoming more frequent.

Objective: Our aims were to describe specific clinical features of hypersensitivity reactions to Patent Blue (Guerbet, Roissy, France), results of the allergy workup, and their consequences for patient management.

Methods: We report a series of 14 clinical cases of dye-induced anaphylaxis recorded between 2004 and 2006 in 4 member centers of a network of French allergoanesthesia outpatient clinics.

Results: Reactions appeared to be relatively severe (6/14 grade III reactions). An average 30 ± 6–minute delay was observed between dye injection and symptom onset. In 9 (65%) patients reactions were sustained for several hours, requiring prolonged continuous epinephrine infusion and transfer to an intensive care unit. Prick test results were positive in 8 patients. In 5 patients prick test results were negative, whereas intradermal test results were positive.

Conclusion: Anesthesiologists and allergologists must be aware of this specific risk and of the clinical characteristics of these reactions, which are usually delayed and long lasting. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: *Patent Blue, dye, allergy, anaphylaxis, prick test, intradermal test, sentinel lymph node*

Vital dyes have been used for many years in a variety of clinical situations.[1-3] As their use for lymphatic mapping and sentinel lymph node biopsy in patients with breast cancer and other malignant tumors has increased, studies and reports of anaphylactic reactions have become more frequent.[4] The mechanism underlying the allergic reaction to Patent Blue (Guerbet, Roissy, France) remains unclear.[5-8] Both direct mast cell activation, basophil activation, or both and cross-linking of specific IgE antibodies are possible causative factors.[5,7,8] This has particular consequences (for anesthesiologists and allergists) regarding the various diagnostic investigations that should be performed not only to confirm dye responsibility but also to increase our knowledge concerning the mechanism of these reactions and our capacity to identify safe dyes for future use in the patient.

Clinical features and evolution of these anaphylactic reactions are peculiar and therefore of importance for the anesthesiologist because they infer specific considerations regarding patient management.

We report a series of 14 clinical cases of dye-induced anaphylaxis recorded between 2004 and 2006 in 4 member centers of the Groupe d'Etude des Réactions Anaphylactiques Peranesthésiques, a network of 40 French allergoanesthesia outpatient clinics organized in 1985 that promotes the surveillance of perioperative allergic reactions to describe their clinical characteristics, identify possible risk factors, and identify responsible drugs.

METHODS

All patients included in this series were referred to one of our centers after an immediate hypersensitivity reaction during sentinel node lymphadenectomy for breast cancer performed after achievement of general anesthesia. Patent Blue V was used for lymphatic mapping in each case. Each patient was investigated in accordance with the practice guidelines for the diagnosis of allergic reactions during the perioperative period.[9] The protocol includes a questionnaire concerning age at the time of the reaction, sex, number of previous anesthetics, history of allergy (atopy, drug, food, or latex hypersensitivity), date of the reaction, and drugs used before the reaction. Details were obtained regarding the degree of the reaction and graded from I to IV in order of increasing severity: grade I, cutaneous signs; grade II, measurable but not life-threatening signs, including cutaneous effects, arterial hypotension (defined as a >30% decrease in blood pressure associated with unexplained tachycardia), cough, or difficulty in mechanical ventilation; grade III, life-threatening reactions (cardiovascular collapse, tachycardia or bradycardia, arrhythmias, and severe bronchospasm); and grade IV, circulatory shock and cardiac arrest, respiratory arrest, or both. Data concerning allergy investigations were systematically recorded: type of skin tests performed (ie, skin prick tests, intradermal tests, or both) and results of plasma histamine and serum tryptase monitoring during the adverse reaction, where available. Plasma concentrations of histamine (RIA Histamine; Immunotech, Marseille, France;

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normal value, <10.8 nmol · L^{-1}; sensitivity, <1 nmol · L^{-1}; reproducibility, 13%) and serum concentrations of tryptase (UniCAP Tryptase; Pharmacia & Upjohn, Saint Quentin en Yvelines, France; normal value, <12 ng · mL^{-1}; sensitivity, <0.2 ng · mL^{-1}; reproducibility, 7%) were determined by using commercially available RIA kits. Skin tests for all the drugs administered during anesthesia were performed as recommended.[9] Undiluted Patent Blue V (2.5%) was used for prick testing. A decreasing dilution scale was used for intradermal testing (starting dose, 1:1000; maximal concentration, 1:10). Skin tests with blue dye have been previously demonstrated as nonirritating by several authors,[10-14] as well as in 9 control patients in our centers.

RESULTS

Information regarding demographics, history, clinical symptoms, and the investigation is summarized in Table I. The mean age was 52.5 ± 3.6 years (range, 22-70 years). A history of food hypersensitivity unrelated to the presence of dyes was present in 3 patients. A history of drug hypersensitivity was reported in 2 patients, among whom 1 patient (Table I, patient 13) reported the onset of a grade III anaphylactic reaction associated with increased circulating histamine concentrations during previous breast surgery. Unfortunately, although Patent Blue had been used during this previous episode, no skin test with this dye had been performed during the first allergy workup. Because many substances used in industry and everyday life contain triphenylmethane-related dyes, each patient included in this study had probable prior exposure to these dyes.[15] Reactions appeared to be relatively severe, with 6 (43%) grade III reactions. Cutaneous signs were almost always observed and were frequently associated with angioedema, whereas respiratory symptoms were reported in only 3 patients. All reactions were relatively delayed after dye injection (mean, 30 ± 6 minutes; minimum, 10 minutes; maximum, 60 minutes) when compared with the usually very rapid onset (classically <10 minutes) of hypersensitivity reactions observed during the perioperative period in case of sensitization to muscle relaxants or antibiotics.[16] Cardiovascular signs (hypotension or cardiovascular collapse) were present in 11 patients. In 9 patients reactions were sustained for several hours, requiring prolonged continuous epinephrine infusion and transfer to an intensive care unit. When measured, circulating histamine concentrations were increased in 6 of 8 patients, and tryptase concentrations were increased in 3 of 9 patients. Skin test results were positive in all patients either by using prick or intradermal tests; however, in 5 patients prick test results were negative, whereas intradermal test results were positive.

DISCUSSION

Hypersensitivity reactions to anesthetics and associated agents used during the perioperative period have been reported with increasing frequency in most developed countries. Their estimated incidence ranges between 1 in 5000 to 1 in 13,000 anesthetics,[17] with the estimated incidence of IgE-mediated immediate hypersensitivity reactions ranging from 1 in 10,000 to 1 in 20,000 anesthetics.[16] Although neuromuscular blocking agents, latex, and antibiotics are the leading causative agents, every substance used during the perioperative period can be responsible for an immediate hypersensitivity reaction.[18]

Since the 1960s, blue dyes have been used in a variety of clinical situations, ranging from cardiac output determination[1] and lymphangiography[19] to intraoperative lymphatic mapping and sentinel lymphadenectomy in various types of neoplasms.[20] They have long been considered a rare cause of anaphylaxis. This might in part be due to misleading nomenclature.[15] Patent Blue V (also called E131, Acid Blue 3, and disulfine blue) and isosulfan blue (also called Patent Blue violet or Lymphazurin), which belong to the group of triarylmethane dyes and share the same formula, are the most commonly used (Fig 1). A recent literature review that includes various names of these dyes reveals an impressive number of case reports of hypersensitivity reactions,[4] and it has been suggested that sensitization occurs with everyday products containing blue dyes.[21] In view of the increasing use of blue dyes for lymphatic mapping for sentinel lymph node biopsy, the incidence of anaphylaxis to these drugs can be expected to increase. Based on several retrospective and prospective studies, the estimated incidence of reactions of all grades of severity varies between 1% and 2%, with severe reactions being observed in 0.2% to 1.1% of cases.[4,22-26] In a series of 1013 patients, preoperative prophylaxis with glucocorticoids, diphenhydramine, and famotidine was found to reduce the severity but not the overall incidence of adverse reactions to dye.[27] Similarly, a nonsignificant trend toward fewer allergic reactions with smaller volumes of blue dye has been reported.[24]

The clinical diagnosis of an immediate hypersensitivity reaction during anesthesia is generally considered difficult. Many signs can be misinterpreted as an interaction between the clinical status of the patient and the drugs administered, a dose-related side effect of the drugs, or excessively light anesthesia. Vigilance is essential because reactions might be well established before they are detected. Therefore information concerning the various clinical features encountered is essential, particularly when reactions caused by injected dye are considered. Indeed, the clinical diagnosis of anaphylaxis is, in fact, presumptive based on a close temporal relation with the administration of the implicated substance. This is clearly not the case for hypersensitivity reactions elicited by dyes. In our series, although the clinical reactions respond to the definition of an "immediate" reaction occurring within less than 1 hour after exposure, they significantly differ from those caused by neuromuscular blocking agents or antibiotics, which usually occur less than 10 minutes after intravenous administration in a sensitized patient.[17] The mean delay observed was about 30 minutes, no reaction was observed in the first 10 minutes after injection, and in 2 patients clinical symptoms were observed 1 hour after dye injection. This might be explained by the kinetics of resorption from the subcutaneous tissue at the site of dye injection.

Another difficulty in the clinical diagnosis of a reaction is the possible interaction between dye and pulse oximetry.[28-31] A decrease in oxygen saturation is an important clinical sign observed in severe anaphylactic shock. However, blue dyes have been reported to interfere with noninvasive pulse oximetry readings. In our experience, in a series of 15 consecutive patients monitored for 2 hours after dye injection, the mean time to the maximum change was 30 minutes. The decrease in pulse oximetry values was relatively limited (mean, 1.5%; SD, 1.8%) but relatively sustained, lasting for the entire study period (unpublished data).

Most clinical cases reported in the literature concern grade I or II reactions, with urticaria, blue hives, and angioedema. However, moderate-to-severe hypotension does occur. This was the case in our series, with 6 patients having grade III reactions. Reactions responded rapidly to treatment but required intravenous epinephrine administration in 11 patients. Moreover, clinical signs appeared to be long-lasting in 6 patients who required prolonged

TABLE I. Adverse reactions to Patent Blue V in patients undergoing lymphatic mapping

Patient no.	Age (y)	Allergies	Preoperative anti-H1	Reaction severity	Interval between dye injection and reaction (min)	Length of symptoms (min)	Clinical reaction	Intraoperative treatment	Postoperative treatment (length of infusion)	Histamine (nmol · L^{-1})*	Tryptase (μg · L^{-1})†	Skin prick test‡	Intradermal test§
1	22	Minocycline, banana, fish	Yes	2	25	180	Urticaria, hypotension	Epinephrine	Epinephrine, 2 h	364	7.7	Positive	1:1000
2	63	None	No	2	15	20	Urticaria, hypotension	Epinephrine	Epinephrine, 4 h	49	9.8	Positive	1:1000
3	52	None	Yes	2	10	2160	Hypotension	Epinephrine	Epinephrine, 2 h	3.4	1.8	Positive	1:1000
4	60	None	No	2	60	1440	Hypotension	Epinephrine	Epinephrine, 24 h	295	3.4	Positive	1:1000
5	64	Noramidopyrine	No	3	60	15	Urticaria, cardiovascular collapse	Epinephrine	None	Not done	24.1	Negative	1:100
6	38	None		3	10	120	Cardiovascular collapse, bronchospasm	Epinephrine	Epinephrine, 2 h	Not done	Not done	Negative	1:100
7	42	None	No	2	50	30	Urticaria, angioedema, hypotension	Corticosteroids, volume expansion	None	Not done	Not done	Positive	1:100
8	42	None	No	3	10	1440	Urticaria, angioedema, cardiovascular collapse, bronchospasm	Epinephrine	Epinephrine, 2 h	Not done	Not done	Negative	1:100
9	54	None	No	2	20	120	Urticaria, hypotension	Epinephrine, volume expansion	Epinephrine, 2 h	248	15.2	Negative	1:1000
10	70	None	No	1	45	15	Urticaria, angioedema	None	None	7.6	3.5	Negative	1:1000
11	50	Pollen, cat	No	3	10	120	Urticaria, angioedema, cardiovascular collapse	Epinephrine, steroids	Epinephrine, 2 h	Not done	Not done	Positive	Not done
12	67	None	No	3	30	30	Urticaria, angioedema, cardiovascular collapse	Epinephrine	None	125	30	Positive	Not done
13	64	Chestnut, grapefruit	No	3	10	60	Urticaria	Epinephrine, volume expansion	Epinephrine, 2 h	245	7.2	Positive	Not done
14	47	None	Yes	2	60	120	Urticaria, angioedema, dyspnea	Corticosteroids	None	Not done	Not done	Not done	1:10

*Histamine: normal value, <9 mmol · L^{-1}.
†Tryptase: normal value, <12 μg · L^{-1}.
‡Skin prick test: positive when wheal is half of that produced by a codeine positive control and at least 3 mm greater than that produced by a saline negative control.
§Intradermal test: positive when wheal at 15 minutes is twice the injection wheal.

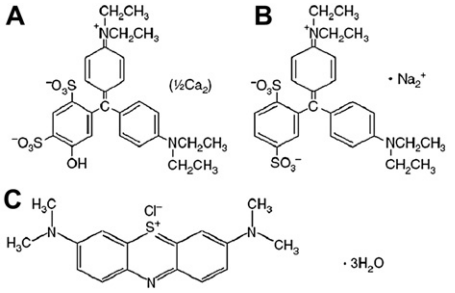

FIG 1. Structural formulas of dyes commonly used for sentinel lymph node localization: **A**, Patent Blue V. **B**, Isosulfan blue. **C**, Methylene blue. Used with permission from Scherer K, Bircher AJ, Figueiredo V. Blue dyes in medicine—a confusing terminology. Contact Dermatitis 2006;54:231-2.[15]

infusion of low-dose epinephrine and monitoring in an intensive care unit. These observations are consistent with previously reported cases described as exhibiting a biphasic reaction.[14,32,33] Both the slow release of the dye from subcutaneous or lymphatic tissue and the several hours' half-life of the dye in the bloodstream have been proposed to explain this sustained duration. Whatever the case, this strongly suggests that prolonged (24 hours) surveillance in the intensive care unit is warranted for patients with hemodynamic symptoms requiring epinephrine administration.

The mechanism underlying the allergic reaction to blue dyes remains unclear.[5-8] Both direct mast cell activation, basophil activation, or both and cross-linking of specific IgE antibodies are possible causative factors.[5,7,8] Evidence supporting an IgE-mediated mechanism, at least in some patients, comes from 2 clinical reports, one demonstrating an immune-mediated mechanism by means of a passive transfer test[5] and the second demonstrating the presence of specific IgE detected by using an ELISA.[7] In addition, in our series, when measured after symptom onset, tryptase circulating concentrations were significantly increased in 2 of 6 patients. Increased tryptase levels are usually regarded as a strong argument in favor of mast cell activation through an IgE-mediated mechanism.[34,35] However, because of a relatively limited negative predictive value, particularly in the case of hypersensitivity reactions of a low severity grade, tryptase concentration within the normal range do not rule out the possibility of a specific immune-mediated mechanism. Therefore our results also favor an IgE-mediated mechanism, at least in some patients.

Histamine circulating concentrations were increased in 6 of 8 patients. In 3 patients a marked increase in histamine levels was observed, whereas tryptase levels remained within the normal range. Also, a normal tryptase level does not rule out a possible IgE-mediated reaction, and these results suggest that direct basophil activation might exist in some patients.

Taken together, the histamine and tryptase measurements we obtained are consistent with previous reports that showed that preoperative prophylaxis was found to reduce the severity of immediate hypersensitivity reactions elicited by dyes, although not the overall incidence.[27,36] Indeed, prophylaxis might be helpful in reducing the severity of symptoms resulting from histamine release, mainly in the case of non–IgE-mediated hypersensitivity reactions, but will be ineffective in preventing IgE-mediated reactions.

Skin tests are usually considered valuable tools in the diagnosis of IgE-mediated hypersensitivity reactions.[37] Both prick and intradermal tests have been proposed in the literature for the diagnosis of sensitization to blue dyes. However, in our series, in 5 patients prick test results were negative, whereas intradermal testing confirmed the responsibility of Patent Blue V. False-negative prick test results have been occasionally reported in the literature.[8,13] Also, prospective skin prick testing with Patent Blue before lymphography has previously been shown to decrease the frequency of hypersensitivity reactions but failed to detect sensitization in all cases.[38] Our results strongly suggest favoring intradermal tests, using up to a 1:100 dilution for the diagnosis of sensitization to blue dyes in patients with a history of a possible immediate hypersensitivity reaction to dyes.

We also recommend systematic testing with methylene blue in case of hypersensitivity to Patent Blue dye. Indeed, methylene blue has also been shown to be an effective dye for sentinel lymph node localization,[11,26,39-41] with only a limited number of complications reported.[42-44] Anaphylactic reactions involving methylene blue seem to be very rare,[45] perhaps because this small molecule does not bind to plasma proteins, thus reducing the risk of sensitization to a hapten-protein complex.[46] This dye differs structurally from isosulfan blue and Patent Blue V. Therefore cross-reactivity is not expected. However, one of our patients had a positive skin test result to both Patent Blue V and methylene blue. Such a sensitization to both Patent Blue and methylene blue, suggesting a possible immunologic cross-reactivity between these dyes, has previously been reported in a series of 3 patients with melanoma.[10] These reports support the systematic investigation of a possible cross-reactivity before the use of an alternate dye. A negative skin test result with methylene blue in the case of a hypersensitivity reaction to Patent Blue V or isosulfan blue might be an argument in favor of using methylene blue for future sentinel lymph node mapping.

In conclusion, the use of Patent Blue V for localization of sentinel lymph nodes is associated with a significant number of hypersensitivity reactions. Anesthesiologists must be aware of this specific risk and of the clinical characteristics of these reactions, which are usually relatively delayed and long lasting and justify a prolonged survey in the intensive care unit when prolonged epinephrine administration is necessary. Histamine and tryptase measurements at the time of the reaction are mandatory to increase our knowledge concerning the mechanism of these reactions. Skin tests are a valuable tool to confirm sensitization against blue dyes, but intradermal tests should be performed in case of negative prick test results. A systematic intradermal test with methylene blue, when the result is negative, might support the recommendation of the use of this dye for future lymph node mapping.

Clinical implications: Intradermal tests should be performed in case of negative prick test results. The use of alternate dyes, such as methylene blue, should be considered.

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