
Anaphylaxis to isosulfan blue

Scot A. Laurie, MD; David A. Khan, MD; Rebecca S. Gruchalla, MD; and George Peters, MD

Background: Isosulfan blue 1% is a dye used in medical procedures such as lymphangiography and sentinel lymph node biopsy. Anaphylactic reactions to this dye have been rarely reported.

Objective: We are reporting two patients who experienced anaphylaxis after subcutaneous administration of isosulfan blue.

Methods: Two female patients with breast cancer were evaluated by our allergy service after suspected intraoperative anaphylactic episodes during sentinel lymph node biopsies in which they had received isosulfan blue 1% for the purpose of visualization of the lymph vessels. In the first case, the patient suffered hypotension and hypoxia requiring intubation. In the second case, the patient suffered prolonged hypotension. Both patients recovered without sequelae. The patients were seen in our clinic, and skin tests were performed to isosulfan blue in addition to other agents the patients had received during anesthesia.

Results: In both cases, the patients demonstrated positive skin tests to isosulfan blue. Neither patient had positive skin tests to any other agent used for skin testing. Isosulfan blue skin tests were performed in nine control subjects and all skin tests in the control subjects were negative.

Conclusions: Isosulfan blue may be a cause of anaphylactic reactions and this seems to be an immunoglobulin E-mediated event as confirmed by positive skin tests.

Ann Allergy Asthma Immunol 2002;88:64–66.

INTRODUCTION

Isosulfan blue (Lymphazurin 1%; United States Surgical Corporation, Norwalk, CT) is a blue dye from the triphenylmethane family. Similar dyes have been used since the 1930s primarily to visualize the lymph vessels before lymphangiography. Recently, isosulfan blue has been used during sentinel lymph node biopsies in breast cancer patients as part of the staging workup of breast cancer. Reactions to this agent are rare and there is only one report of anaphylaxis caused by isosulfan blue found in the literature.¹ In this case, there was no investigation to evaluate the possibility of an immunoglobulin (Ig)E-mediated event as a mechanism of anaphylaxis. We report the first two cases of isosulfan blue anaphylaxis with support for an IgE-

mediated mechanism provided by positive skin tests.

CASE 1

A 60-year-old woman with stage II carcinoma of the right breast underwent a sentinel lymph node biopsy. Approximately 5 minutes after the subcutaneous administration of 5 mL of isosulfan blue, she developed hypotension, hypoxemia (oxygen saturation 74%), wheezing, and diffuse urticaria. She required three intravenous doses of epinephrine 1 μ g, followed by two intravenous 10- μ g doses. She was emergency intubated. The patient's blood pressure gradually normalized and she was extubated 4 hours later, recovering without sequelae.

Her drug allergy history was remarkable for a maculopapular rash with penicillin and local swelling with lidocaine after a dental procedure. She had no previous history of exposure to isosulfan blue.

Skin prick testing was performed to the drugs she received before her anaphylactic episode: propofol 10 mg/mL,

fentanyl 50 μ g/mL, lidocaine, and isosulfan blue 1%. Intradermal tests were also performed with propofol and fentanyl in stepwise fashion, using serial 10-fold dilutions from 1:10,000 to 1:10. Lidocaine intradermal testing was performed at a 1:100 dilution. Ciprofloxacin intradermal testing was performed using a 1:100,000,000 dilution. Isosulfan blue intradermal testing used 1:10,000 and 1:1,000 dilutions. Penicillin skin testing was also electively performed. Both skin prick and intradermal tests were positive to isosulfan blue (Table 1), whereas all other skin prick and intradermal tests were negative.

Isosulfan blue intradermal skin testing was performed on 8 healthy and 1 breast cancer patient with no history of isosulfan blue reaction or exposure to isosulfan blue. No subjects reacted at the 1:1,000 or 1:100 dilutions of isosulfan blue. Skin prick testing using isosulfan blue was not performed in the control subjects.

The patient underwent sentinel lymph node lymphadenectomy and right partial mastectomy without the use of isosulfan blue 2 days after her positive skin test. She again received propofol, midazolam, lidocaine, and fentanyl before her procedure and received cefazolin 1 g intravenously for perioperative antibiotic prophylaxis and tolerated all medications without any adverse events noted.

CASE 2

A 62-year-old woman with breast cancer was undergoing a bilateral sentinel lymph node biopsy. Approximately 40 minutes after the start of the procedure, she developed hypotension and tachycardia. The patient did not manifest wheezing, desaturation, or urticaria. Despite treatment with phenylephrine ($4 \times 100 \mu$ g), her hypotension (70/40 mm Hg) persisted for approximately 30 minutes. She was transferred to the

The University of Texas Southwestern Medical Center, Department of Internal Medicine, Division of Allergy and Immunology, Dallas, Texas. Received for publication March 1, 2001.

Accepted for publication in revised form July 24, 2001.

Table 1. Isosulfan Blue Skin Testing

Patients	Prick test isosulfan blue 1%	ID 1:10,000		ID 1:1000		ID 1:100		Positive control: histamine 1 M (184 mg/mL) prick	Negative control: saline		
	15 min	0 min	15 min	0 min	15 min	0 min	15 min	15 min	Prick	ID	
									15 min	0 min	15 min
Patient 1	4 × 3	5 × 5	5 × 6	4 × 4	8 × 6*	Not done		11 × 9	0	5 × 5	0 × 0
Patient 2	4 × 3	3 × 3	3 × 3	4 × 4	4 × 5	4 × 3	7 × 7*	8 × 8	0	3 × 4	1 × 2

Notes: All measurements are given in mm.

* Denotes a positive intradermal test. An increase in wheal size of 2 × 2 mm after 15 minutes is considered positive.

Intradermal testing using Isosulfan blue 1% in [1:1,000] and [1:100] dilutions was performed in 9 subjects and all were negative.

intensive care unit for observation and she recovered without sequelae. An unfractionated serum tryptase was obtained 30 minutes after her intraoperative hypotensive event and was elevated at 37.9 ng/mL (normal range is 0 to 11.5 ng/mL).

Her drug allergy history included a reaction to penicillin approximately 5 years before, consisting of tongue swelling, hives, and emesis. She had no history of previous exposure to isosulfan blue.

Three weeks before her reaction, she had undergone needle localization and biopsy of the breast mass. She had received propofol, lidocaine, midazolam, and fentanyl and tolerated that procedure without difficulty. She again received those agents along with cefazolin and isosulfan blue at the onset of her sentinel lymph node biopsy.

Skin prick testing to cefazolin 100 mg/mL, isosulfan blue 1%, and penicillin was performed. Intradermal testing was then performed using cefazolin and isosulfan blue in serial 10-fold dilutions from 1:10,000 to 1:100. Skin prick and intradermal tests were positive to isosulfan blue (Table 1). Cefazolin and penicillin skin tests were negative.

The patient underwent subsequent lymph node biopsy and bilateral partial mastectomies without isosulfan blue. She again received propofol, fentanyl, midazolam, and lidocaine, along with cefazolin for perioperative antibiotic

prophylaxis, and tolerated the procedure without any adverse events.

DISCUSSION

Isosulfan blue is a safe and efficacious drug for the identification of lymph vessels during lymphangiography and was the first dye to be approved by the Food and Drug Administration for that purpose.² In the past, reports of allergic reactions to blue dyes have been made.³⁻⁵ Severe reactions have been reported, but these studies used unstandardized dye concentrations, dosages, or used the dye with other drugs.^{4,6} In phase III clinical trials of isosulfan blue, there were no serious reactions reported in 543 adults when a standard concentration of 1% was used without local anesthetics.² Five of the 543 subjects had undefined mild allergic reactions within 15 minutes after the administration of isosulfan blue. All patients received no or minimal symptomatic therapy and recovered in 1 hour or less. It should be noted that 4 of these 5 patients received blue dye admixed with local anesthetic, thus raising the possibility that these mild reactions may be attributable to the local anesthetic. When isosulfan blue is used in the proper 1% concentration without local anesthetics, the risk of a severe reaction is low.¹

We attribute the first two cases of anaphylaxis to isosulfan blue 1%, in which both patients exhibited positive skin tests to the blue dye. Based on the

clinical spectrum along with the positive skin tests, we conclude that anaphylaxis to isosulfan blue is likely an IgE-mediated event. Given the relatively small molecular weight of isosulfan blue, it likely acts as a hapten. Neither of our patients had previous exposure to isosulfan blue, leading us to speculate that sensitization occurs through exposure to a cross-reactive antigen. In both cases, our patients had histories of penicillin allergy but were penicillin-skin test negative. Penicillins are not structurally related to triphenylmethane dyes. One drug with a related structure is phenolphthalein,⁷ which is widely available as a laxative, but any relationship of that drug to these reactions is speculative, and it is unknown whether either of these patients was ever exposed to phenolphthalein.

CONCLUSION

With the increasing use of isosulfan blue in diagnostic procedures, surgeons, radiologists, and allergists should be aware of the possibility of anaphylaxis to isosulfan blue.

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- Requests for reprints should be addressed to:*
David A. Khan, MD
UT Southwestern Medical School
Dallas, TX 75390-8859
E-mail: david.khan@utsouthwestern.edu
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