

Case Report: Isosulfan Blue–Related Anaphylaxis

LCDR Jacob Adams, MC, USN^{*}; CPT Jonathan Goc, MC, USA^{*}; CPT Justin Zeien, MC, USA^{ID*};
Alpesh Patel, MD[†]; Josephine Gambardella, MD^{‡,†}

ABSTRACT Anaphylaxis is an acute multisystem syndrome typically resulting from the sudden release of mast cell and basophil-derived mediators into the circulatory system. Isosulfan blue dye is a rare, but known, mediator of anaphylaxis with an incidence between 0.16% and 2% of cases. We report two cases of anaphylaxis attributed to the use of isosulfan blue dye in the intraoperative setting. Both of the patients we report had grade 3 anaphylactic reactions requiring vasopressors to correct significant hypotension. Both patients required overnight monitoring in the intensive care unit with the second patient also requiring continued vasopressor support.

INTRODUCTION

Anaphylaxis is an acute multisystem syndrome typically resulting from the sudden release of mast cell and basophil-derived mediators into the circulatory system.^{1,2} Anaphylaxis applies to immunoglobulin E (IgE)-dependent mechanisms, which account for 60% of perioperative anaphylaxis,³ non-IgE-dependent immunologic mechanisms, and non-immunologic mechanisms.^{4,5} The incidence of anaphylaxis in general anesthesia is 1:1,250 to 1:18,600.⁶ The most common identifiable causes of perioperative anaphylaxis are antibiotics, blood products, chlorhexidine, neuromuscular blocking agents, sugammadex, hypnotic agents, opioids, colloids, and latex.⁷ Clinical signs and symptoms of anaphylaxis include pruritus, shortness of breath, hypotension, bronchospasm, laryngeal edema, tachycardia or bradycardia, cyanosis/oxygen desaturation, and reduced or absent capnography tracing.⁸ Cardiovascular collapse is the first detected manifestation in up to 50% of cases.^{1,7} We present two cases of anaphylaxis attributed to the use of isosulfan blue dye in the intraoperative setting. These patients have provided written HIPAA authorization to publish these case reports.

CASE REPORTS

The first case involved a 17-year-old female who was scheduled for melanoma excision from her right upper extremity with a sentinel lymph node biopsy. She had no history of drug allergies, and her past medical history was only significant for melanoma and acne vulgaris. Two hours before surgery,

four aliquots of 0.1 mL of 0.5 mCi technetium-99m-labeled sulfur colloid radiotracer were injected intradermally around the melanoma. One hour before surgery, she received premedication as part of a multimodal, opioid-sparing analgesic approach to reduce intraoperative and postoperative analgesic requirements along with facilitating expedited recovery after surgery. The premedication included 400 mg of gabapentin, 650 mg of oral acetaminophen, 100 mg of oral celecoxib, and 20 mg of intravenous famotidine. The preoperative course was uneventful. Induction of anesthesia entailed intravenous injection of 100 mg of lidocaine, 100 µg of fentanyl, and 200 mg of propofol. Because of copious clear secretions in the patient's mouth, her airway was thoroughly suctioned, and 0.1 mg of glycopyrrolate was intravenously administered. A laryngeal mask airway was then placed for airway support. Three minutes after induction of anesthesia, 2 g of cefazolin was administered intravenously in addition to 6 mg of dexamethasone for postoperative nausea and vomiting prophylaxis. Nine minutes after induction of anesthesia, 2 mL of isosulfan blue dye was intradermally injected in the four quadrants around the right upper arm melanoma and massaged for 5 minutes. Sixteen minutes after injection of isosulfan blue dye, a local anesthetic mixture consisting of 10 mL of 1% lidocaine with 1:200,000 epinephrine and 10 mL of 0.25% bupivacaine with 1:200,000 epinephrine was injected subcutaneously into the right axillary area. Eighteen minutes after injection of isosulfan blue dye, the patient became hypotensive to 60/35 mm Hg with a heart rate in the low 80s. Her blood pressure did not increase after three intravenous boluses of phenylephrine for a total of 800 µg over a 10-minute period. The anesthesia provider notified the surgeon of the patient's persistent hypotension and called for assistance from additional anesthesiologists. The anesthesia and surgical teams agreed to pause the surgery. The patient was noted to have swelling in her upper extremities, face, neck, and ears at that time. Over the next 15 minutes, the patient was treated with a 1.5-L bolus of Lactated Ringers, 1 g of intravenous calcium, 50 mg of intravenous diphenhydramine, 10 mg of intravenous dexamethasone, two units of intravenous vasopressin, and 30 µg of intravenous epinephrine. While receiving the aforementioned treatments, the patient's heart rate increased to a maximum

^{*}Department of Anesthesiology, Walter Reed National Military Medical Center, Bethesda, MD 20889, USA

[†]Department of Anesthesiology, Inova Fairfax Medical Campus, Falls Church, VA 22042, USA

[‡]Department of Anesthesiology, University of Virginia School of Medicine, Falls Church, VA 22903, USA

The views expressed in this material are those of the authors and do not reflect the official policy or position of the U.S. Government, the DoD, the Department of the Army, or the Department of the Navy.

doi:<https://doi.org/10.1093/milmed/usac419>

Published by Oxford University Press on behalf of the Association of Military Surgeons of the United States 2023. This work is written by (a) US Government employee(s) and is in the public domain in the US.

of 155 and plateaued in the 110s. The patient remained hypotensive to 60s-70s/30s-40s for a total of 20 minutes, but, eventually, these treatments increased the patient's blood pressure to 150/90 with a heart rate in the low 100s. Oxygen saturation, tidal volumes, and peak airway pressures were unchanged throughout the event. After a discussion between the anesthesia provider and the surgeon, there was an agreement to resume the surgery for two reasons: (1) The surgery was close to completion with the most stimulating portions of the surgery already finished and (2) the patient was hemodynamically stable with minimal concern for recurrence of hemodynamic compromise. The anesthesia provider was prepared with intravenous epinephrine boluses and an epinephrine infusion in case of recurrence of hypotension. Upon removal of the surgical drapes at the end of the case, diffuse total body swelling was noted. Postoperatively, while in the postanesthesia care unit, the patient's blood pressure dropped to 65/40 mm Hg, and her heart rate decreased to 50. After 10 mg of intravenous ephedrine, 25 mg of intravenous diphenhydramine, and a 1.2-L bolus of Lactated Ringers, her blood pressure and heart rate normalized to 145/70 mm Hg and 70, respectively. Laboratory investigations postoperatively were unremarkable except for an elevated tryptase level of $13 \mu\text{g mL}^{-1}$ (normal $<11 \mu\text{g mL}^{-1}$); slightly elevated white blood count and glucose; and slightly lower than normal CO_2 , total protein, albumin, and alkaline phosphatase. The patient had an uneventful overnight stay in the intensive care unit (ICU) where the diffuse swelling resolved and she had no further hypotensive episodes. She was discharged from the hospital the following day.

The second case involved a 62-year-old female who was scheduled for bilateral sentinel lymph node excision for breast cancer staging. She had no history of drug allergies, and her past medical history was significant for the aforementioned breast cancer along with osteosarcoma previously treated with chemotherapy and radiation, intermittent chemotherapy-induced neuropathic pain in her distal extremities, depression, hypothyroidism, and brachial plexitis. The preoperative course was uneventful. Induction of anesthesia entailed intravenous injection of 50 μg of fentanyl, 50 mg of lidocaine, and 150 mg of propofol. A laryngeal mask airway was then placed for airway support. Three minutes after induction of anesthesia, 2 g of cefazolin was intravenously administered to the patient. Five minutes after induction of anesthesia, 3 mL of isosulfan blue dye was injected subcutaneously into the patient's right breast, deep into the areola. Immediately afterward, a local anesthetic mixture consisting of 10 mL of 1% lidocaine with 1:200,000 epinephrine and 10 mL of 0.25% bupivacaine with 1:200,000 epinephrine was injected subcutaneously around the surgical field. Twenty-seven minutes after induction of anesthesia, the patient became hypotensive to 57/38 mm Hg with a heart rate of 92. Her blood pressure did not increase after three intravenous boluses of phenylephrine (600 μg over an 8-minute period). Surgery was paused at this time. The patient was treated with a 600-mL bolus of

Lactated Ringers, 4 mg of intravenous dexamethasone, 50 mg of intravenous diphenhydramine, six units of intravenous vasopressin, 125 mg of intravenous methylprednisolone, 300 μg of intravenous epinephrine, and an epinephrine infusion of $10 \mu\text{g min}^{-1}$. While receiving these treatments, the patient's heart rate stayed in the 90s to low 100s. The patient remained hypotensive to 60s-70s/40s-50s for a total of 40 minutes. After this time, the treatments increased the patient's blood pressure to 95/65 mm Hg with a heart rate of 90. Oxygen saturation, tidal volumes, and peak airway pressures were unchanged throughout the event. After a discussion between the anesthesia provider and surgeon, it was decided to complete the surgery for several reasons: (1) This procedure was deemed time-sensitive in light of the patient's (presumed) advanced cancer, and rescheduling the staging procedure would delay treatment and could worsen future recovery outcomes; (2) the surgery was close to completion; and (3) despite requiring a low-dose epinephrine infusion, the anesthesia provider determined the patient was hemodynamically stable enough and they felt comfortable allowing the surgery to finish. Upon completion of the surgery, the patient was transported to the ICU with an epinephrine infusion running at $10 \mu\text{g min}^{-1}$ and remained hemodynamically stable. Laboratory investigations were not drawn. She remained on the epinephrine infusion in the ICU and had an uneventful overnight stay without additional hypotensive episodes. On the first postoperative day, she underwent a full cardiac workup, including a bedside echocardiogram, which did not reveal any significant abnormalities. She was discharged from the hospital later that day. Of note, this patient underwent another surgical procedure approximately 2 weeks later and received the same medications for induction of anesthesia and the same antibiotics. However, she did not receive isosulfan blue dye and did not have recurrence of anaphylaxis.

DISCUSSION

Numerous reports of anaphylactic reactions to isosulfan blue dye exist with the current estimated incidence between 0.16 and 2% of cases.⁹⁻¹¹ Mortality secondary to anaphylactic reactions to isosulfan blue dye is exceedingly rare and has not been demonstrated in several studies.⁹⁻¹¹ However, mortality estimates because of perioperative anaphylaxis range from 1.4% to 6%, with another 2% of patients surviving with anoxic cerebral injury.¹² Three grades of allergic reactions to isosulfan blue dye have been described. Grade 1 reactions only involve skin symptoms such as urticaria, pruritus, hives, or a generalized rash. Grade 2 reactions include transient hypotension (defined as systolic blood pressure >70) not requiring vasopressor support. Grade 3 reactions include hypotension (systolic blood pressure <70) requiring vasopressor support.¹¹ In our two reported cases, both patients had grade 3 reactions because of the significant hypotension they experienced and the need for vasopressors. Although the literature reports severe (i.e., grade 3) anaphylactic reactions to isosulfan blue dye, milder allergic reactions likely occur more

frequently than the reported 0.16%-2% range.¹³ Regardless, routine pretreatment for patients receiving isosulfan blue dye is not currently standard practice.¹⁴ However, some studies have suggested pretreatment with steroids or antihistamines or even skin testing before the procedure, particularly for high-risk patients with allergies similar to isosulfan blue dye or a history of asthma.¹³ The decision to pretreat or perform skin testing before surgery is further complicated by the fact that the pathophysiology of these adverse reactions is not well defined. The release of basophil-derived mediators from mast cells that drive these adverse reactions can be IgE immune-mediated, non-IgE (IgG or IgM) immune-mediated, or due to direct activation of mast cells.¹⁵ Non-IgE-mediated and direct activation of mast cells are termed pseudo-allergic reactions and prevented by pretreatment with steroids or antihistamines.¹⁵ IgE-mediated mast cell degranulation is the mechanism behind true anaphylactic reactions,¹⁵ and currently, there are no studies demonstrating effective pretreatments in humans.

It is often difficult to identify a causative agent for perioperative anaphylaxis as there is no definitive test to prove or disprove anaphylaxis. In one study, a causative agent was discovered in only 24% of patients with the most common culprit being antibiotics, particularly cefazolin.¹⁵ Skin testing has been described but is limited by the simultaneous administration of multiple different drugs in the intraoperative setting, making it difficult to determine which drug(s) to test, along with allergists often lacking familiarity with these drugs.¹⁶ Tryptase levels have also been described, but their collection after an allergic reaction is time-sensitive and the lack of a baseline value significantly decreases their sensitivity.¹⁶ Even when patients who experienced perioperative anaphylaxis undergo subsequent anesthesia, the overwhelming majority do not have another perioperative allergic reaction.¹⁵ In the first case, isosulfan blue was the presumed cause of the patient's anaphylactic reaction because of the close temporal relationship between subcutaneous injection of isosulfan blue and onset of hemodynamic instability. However, the authors recognize the possibility of cefazolin (or another medication administered either during induction of anesthesia or at the beginning of the surgery) serving as the inciting factor for anaphylaxis, particularly because of the higher incidence of anaphylaxis associated with these other medications, especially cefazolin, and the similar close temporal relationship between their administration and onset of hemodynamic instability. In the second case, isosulfan blue was the presumed cause of the patient's anaphylaxis for similar reasons as the first case in addition to the lack of intraoperative anaphylaxis experienced by the patient 2 weeks later during a surgery in which she received the same medications, including cefazolin, except isosulfan blue. Yet, as previously mentioned, some patients who experience perioperative anaphylaxis do not experience anaphylaxis again when exposed to the same inciting medication. The authors again recognize

the possibility of cefazolin or another medication administered around the same time frame as isosulfan blue serving as the causative agent of anaphylaxis.

A high index of suspicion is required to quickly identify and treat anaphylaxis while under general anesthesia as the presenting symptoms may include cardiovascular collapse, hypotension, bronchospasm, tachycardia, and laryngeal edema.¹² In both of the cases reported, hypotension was the initial presenting sign with total body swelling and tachycardia also noted in the first patient. Both patients had no noticeable respiratory symptoms or signs. The differential diagnosis can be broad and include other causes of these cardiorespiratory symptoms. Cardiovascular collapse may be caused by hemorrhage, cardiogenic shock, arrhythmias, sympathectomy from neuraxial anesthesia, local anesthetic systemic toxicity, sepsis, and venous air embolism. Hypoxia, increased airway pressures, and ventilation difficulties may be caused by acute asthma exacerbation, aspiration, malignant hyperthermia, pulmonary embolism, pulmonary edema, pneumothorax, and transfusion-related acute lung injury. Early recognition of the signs of anaphylaxis in the intraoperative setting and prompt initiation of treatment are crucial to achieve better outcomes.¹⁷ The suggested initial and secondary steps for the management of anaphylaxis while under general anesthesia can be seen in Table I.¹⁸

In both cases, although anaphylaxis was not the clear diagnosis initially, the hypotension was treated promptly and aggressively. Once the patient is stable, a discussion with the surgeon is recommended to determine if it is necessary to continue with the procedure and postoperative disposition. The

TABLE I. Initial Management of Anaphylaxis During General Anesthesia

Initial therapy
• Stop administration of antigen • Maintain airway and administer 100% O₂ • Discontinue all anesthetic agents • Start intravascular volume expansion (2-4 L of crystalloid/colloid with hypotension) • Give epinephrine (5-10 µg intravenous bolus with hypotension, titrate as needed; 0.1-1.0 mg intravenous with cardiovascular collapse)
Secondary treatment
• Antihistamines (0.5-1 mg kg⁻¹ diphenhydramine) • Catecholamine infusions (starting doses: epinephrine 4-8 µg min⁻¹, norepinephrine 4-8 µg min⁻¹, or isoproterenol 0.5-1 µg min⁻¹ as an infusion, titrated to desired effects) • Bronchodilators: inhaled albuterol, terbutaline, and/or anticholinergic agents with persistent bronchospasm) • Corticosteroids (0.25-1 g hydrocortisone; alternatively, 1-2 g methylprednisolone) • Sodium bicarbonate (0.5-1 mEq kg⁻¹ with persistent hypotension or acidosis) • Airway evaluation (before extubation) • Refractory shock: vasopressin and additional monitoring/echocardiography

decision to continue the procedure is typically determined by weighing the severity of the anaphylactic reaction and the patient's condition against the urgency of the procedure.^{3,19} The surgeries in both reported cases were paused after discussion with the surgeon but allowed to proceed once hemodynamic stability was achieved. Disposition typically includes close monitoring for 24–48 hours, depending on the severity of the reaction and the patient's recovery course.³ In our cases, the first patient was admitted to the ICU overnight because of concern for recurrence of hypotension as evidenced in the postanesthesia care unit. The second patient was admitted to the ICU because of the need for continued vasopressor support. Ultimately, both patients experienced good outcomes as a result of the decisive actions of the anesthesia providers and the effective communication among the perioperative teams.

ACKNOWLEDGMENTS

Not applicable.

FUNDING

The authors received no funding for this work.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY

Not applicable.

CLINICAL TRIAL REGISTRATION

Not applicable.

INSTITUTIONAL REVIEW BOARD (HUMAN SUBJECTS)

Not applicable.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC)

Not applicable.

INSTITUTIONAL CLEARANCE

Not applicable.

INDIVIDUAL AUTHOR CONTRIBUTION STATEMENT

J.Go. and J.Z. gathered resources and background information and drafted the case report. J.A. reviewed, edited formatting, and added table. J.Ga. and A.P. were a part of original case and provided oversight and formatting guidance. All authors read and approved the final manuscript.

REFERENCES

1. Sampson HA, Munoz-Furlong A, Bock SA, et al: Symposium on the definition and management of anaphylaxis: summary report. *J Allergy Clin Immunol* 2005; 115(3): 584–91. [10.1016/j.jaci.2005.01.009](https://doi.org/10.1016/j.jaci.2005.01.009).

2. Lieberman P: Mechanisms of anaphylaxis beyond classically mediated antigen- and IgE-induced events. *Ann Allergy Asthma Immunol* 2017; 118(3): 246–8. [10.1016/j.anaai.2017.01.009](https://doi.org/10.1016/j.anaai.2017.01.009).
3. Mertes PM, Malinovsky JM, Jouffroy L, et al: Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Investig Allergol Clin Immunol* 2011; 21(6): 442–53.
4. Genovese A, Stellato C, Marsella CV, et al: Role of mast cells, basophils and their mediators in adverse reactions to general anesthetics and radiocontrast media. *Int Arch Allergy Immunol* 1996; 110(1): 13–22. [10.1159/000237305](https://doi.org/10.1159/000237305).
5. Veien M, Szlam F, Holden JT, et al: Mechanisms of nonimmunological histamine and tryptase release from human cutaneous mast cells. *Anesthesiology* 2000; 92(4): 1074–81. [10.1097/00000542-200004000-00026](https://doi.org/10.1097/00000542-200004000-00026).
6. Mertes PM, Volcheck GW, Garvey LH, et al: Epidemiology of perioperative anaphylaxis. *Presse Med* 2016; 45(9): 758–67. [10.1016/j.lpm.2016.02.024](https://doi.org/10.1016/j.lpm.2016.02.024).
7. Mertes PM, Laxenaire MC, Alla F, et al: Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999–2000. *Anesthesiology* 2003; 99(3): 536–45. [10.1097/00000542-200309000-00007](https://doi.org/10.1097/00000542-200309000-00007).
8. Harper NJN, Cook TM, Garcez T, et al: Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; 121(1): 159–71. [10.1016/j.bja.2018.04.014](https://doi.org/10.1016/j.bja.2018.04.014).
9. Perenyi M, Barber ZE, Gibson J, et al: Anaphylactic reaction rates to blue dyes used for sentinel lymph node mapping: systematic review and meta-analysis. *Ann Surg* 2021; 273(6): 1087–93. [10.1097/SLA.0000000000004061](https://doi.org/10.1097/SLA.0000000000004061).
10. Cimmino VM, Brown AC, Szocik JF, et al: Allergic reactions to isosulfan blue during sentinel node biopsy—a common event. *Surgery* 2001; 130(3): 439–42. [10.1067/msy.2001.116407](https://doi.org/10.1067/msy.2001.116407).
11. Montgomery LL, Thorne AC, Van Zee KJ, et al: Isosulfan blue dye reactions during sentinel lymph node mapping for breast cancer. *Anesth Analg* 2002; 95(2): 385–8. [10.1213/00000539-200208000-00026](https://doi.org/10.1213/00000539-200208000-00026).
12. Gibbs NM, Sadleir PH, Clarke RC, et al: Survival from perioperative anaphylaxis in Western Australia 2000–2009. *Br J Anaesth* 2013; 111(4): 589–93. [10.1093/bja/aet117](https://doi.org/10.1093/bja/aet117).
13. Sajjan A, Griep DW, Hakmi H, et al: Isosulfan blue and anaphylaxis. *Ochsner J* 2021; 21(4): 419–24. [10.31486/toj.20.0162](https://doi.org/10.31486/toj.20.0162).
14. Raut CP, Daley MD, Hunt KK, et al: Anaphylactoid reactions to isosulfan blue dye during breast cancer lymphatic mapping in patients given preoperative prophylaxis. *J Clin Oncol* 2004; 22(3): 567–8. [10.1200/JCO.2004.99.276](https://doi.org/10.1200/JCO.2004.99.276).
15. Banerji A, Bhattacharya G, Huebner E, et al: Perioperative allergic reactions: allergy assessment and subsequent anesthesia. *J Allergy Clin Immunol Pract* 2021; 9(5): 1980–91. [10.1016/j.jaip.2020.11.025](https://doi.org/10.1016/j.jaip.2020.11.025).
16. Garvey LH, Ebo DG: Perioperative hypersensitivity reactions: time for collaboration. *J Allergy Clin Immunol Pract* 2021; 9(5): 1992–3. [10.1016/j.jaip.2021.02.025](https://doi.org/10.1016/j.jaip.2021.02.025).
17. Lieberman P, Nicklas RA, Oppenheimer J, et al: The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol Pract* 2010; 126(3): 477–80. [doi: 10.1016/j.jaci.2010.06.022](https://doi.org/10.1016/j.jaci.2010.06.022).
18. Levy JH: The allergic response. In: Barash PG, Cullen BF, Stoelting RK et al, eds. *Clinical Anesthesia*. 8th ed. Wolters Kluwer; 2017:212–3.
19. Sadleir PHM, Clarke RC, Bozic B, et al: Consequences of proceeding with surgery after resuscitation from intra-operative anaphylaxis. *Anaesthesia* 2018; 73(1): 32–9. [10.1111/anae.14106](https://doi.org/10.1111/anae.14106).