Isosulfan Blue and Anaphylaxis

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Background: Isosulfan blue dye, or Lymphazurin, is commonly used for sentinel lymph node biopsy during operative procedures for patients with breast cancer. Allergic reactions to Lymphazurin have been reported, ranging from mild dermatologic reactions to severe anaphylaxis.

Case Series: We report 2 patients who experienced allergic reaction to Lymphazurin while admitted to our service. We also conducted a literature search for similar cases using national databases. Included studies were limited to retrospective studies, case series, or case reports. Patient characteristics, reaction observed, and hospital course were extracted. Of the patients we report, both had grade 3 anaphylactic reactions requiring vasopressors to achieve hemodynamic stability. One patient required intensive care unit monitoring for 18 hours, and the other required overnight monitoring in the postanesthesia care unit. The literature revealed 29 studies reporting 108 patients with confirmed allergic reactions to Lymphazurin. Including the 2 patients in this series (total study n = 110), most reactions were grade 3 (57/110, 51.8%), followed by grade 1 (40/110, 36.4%) and grade 2 (13/110, 11.8%). Among the patients who had individual hospital course reported (n = 34), 23 patients required admission to the surgical intensive care unit. Of studies that reported cancellation or progression of surgery after the reaction, the surgical procedure was canceled for 12 of 26 patients (46.1%).

Conclusion: Although severe anaphylactic reactions are more commonly reported, mild reactions occur more frequently but are likely underreported. Although no fatalities were reported in the cases included in this review, anaphylactic reactions to Lymphazurin pose significant risks. Operating room personnel should be familiar with potential reactions to recognize and treat them early.

Keywords: Anaphylaxis, contrast, isosulfan blue
Five minutes after administering Lymphazurin and before the first incision, the patient became tachycardic to the 120/min range, and systolic blood pressure dropped to 75 mmHg. Shortly after, the patient appeared flushed with swollen distal extremities, suggestive of an anaphylactic reaction. Her systolic pressure was mildly responsive to 2 doses of phenylephrine 100 μg and reached as low as 60 mmHg approximately 10 minutes after the initial reaction. She was given 100 μg epinephrine, as well as injections of 50 mg diphenhydramine and 100 mg hydrocortisone. Given her compromised hemodynamic status, the patient was successfully intubated with an endotracheal tube, and the planned procedure was canceled. Table 1 summarizes the pharmacologic agents administered, including those given after the decision was made to cancel the surgery.

The patient was transferred to the surgical intensive care unit (SICU) and closely monitored. She remained intubated overnight and was weaned off the vasopressors by the morning. On hospital day 1, she was extubated and downgraded without issues. She was discharged on hospital day 2 with 20 mg famotidine and a 20 mg hydrocortisone taper. Despite multiple attempts to contact the patient, she was lost to follow-up and did not undergo allergy testing.

### DISCUSSION

Reports of allergic reactions to patent blue dye (parent molecule of isosulfan blue dye) trace back to 1966 when Kopp described 2 cases of anaphylaxis during lymphangiography. The US Food and Drug Administration approved isosulfan blue dye for lymphatic mapping in 1982, and a case report in the same year by Rubis et al was the first to report an allergic reaction specific to Lymphazurin. The reported cases have increased over the years, ranging from self-resolving erythema or urticaria to complicated cases of cardiovascular or respiratory collapse requiring SICU monitoring. The current estimated incidence of adverse reactions to isosulfan blue dye is as high as 2.5%. The pathophysiology of adverse reactions to isosulfan blue dye is not well understood. The anaphylactic reaction involves development of immunoglobulin E antibodies against foreign material. The antigen causes cross-linking and degranulation of mast cells, resulting in the release of histamine and other vasoactive mediators of anaphylaxis. Other postulated mechanisms include disorders in the arachidonic acid metabolism, direct activation of mast cells, and idiopathic anaphylaxis.

Montgomery et al classified the range of adverse reactions secondary to isosulfan blue dye into 3 grades. Grade 1...
Table 2. Outpatient Allergy Skin Testing Results for Case 2

| Product                             | Prick, mm | Intradermal, mm | Result            |
|-------------------------------------|-----------|-----------------|-------------------|
| Histamine                           | 4.8       | 10.21           | Positive control  |
| Diluent control                     | 0.0       | 0.0             | Negative control  |
| Midazolam, 0.5 mg/mL                | 0.0       | 0.0             | Negative          |
| Midazolam, 1:100                    | 0.0       |                 | Negative          |
| Midazolam, 1:10                     | 0.0       |                 | Negative          |
| Fentanyl, 0.05 mg/mL                | 0.0       |                 | Negative          |
| Fentanyl, 1:1,000                   | 0.0       |                 | Negative          |
| Fentanyl, 1:100                     | 0.0       |                 | Negative          |
| Propofol, 10 mg/mL                 | 0.0       |                 | Negative          |
| Propofol, 1:100                    | 0.0       |                 | Negative          |
| Propofol, 1:10                      | 0.0       |                 | Negative          |
| Cefazolin, 330 mg/mL               | 0.0       |                 | Negative          |
| Cefazolin, 1:100                   | 0.0       |                 | Negative          |
| Cefazolin, 1:10                     | 0.0       |                 | Negative          |
| PRE-PEN (benzylpenicilloyl polysine: 10,000 U/mL) | 0.0 | 0.0 | Negative |
| Penicillin G, (benzylpenicillin: 10,000 U/mL) | 0.0 | 0.0 | Negative |
| Lidocaine 2%, 20 mg/mL             | 0.0       |                 | Negative          |
| Lidocaine, 1:100                   | 0.0       |                 | Negative          |
| aIsosulfan blue 1%, 10 mg/mL       | 6.8       |                 | Positive          |
| aIsosulfan blue 1%, 10 mg/mL       | 5.5       |                 | Positive          |
| Isosulfan blue, 1:10,000           | 0.0       |                 | Negative          |
| Isosulfan blue, 1:1,000            | 11.22     |                 | Positive          |

Note: Table shows negative skin testing to PRE-PEN and Penicillin G via intradermal and percutaneous methods with appropriate positive and negative controls. The patient tested negative to midazolam, fentanyl, propofol, cefazolin, and lidocaine but positive to isosulfan blue.

*Test was repeated to confirm reaction to isosulfan blue.

is the simplest reaction and includes urticaria, pruritus, and at times, a rash with or without hives. Grade 2 involves transient hypotension not requiring vasopressors, and grade 3 involves hypotension requiring vasopressors. In the present case series, both patients had grade 3 reactions that required vasopressors and close hemodynamic monitoring.

Review of the literature using national databases (Medline, Embase, and Cochrane) revealed 29 studies reporting 108 patients who had confirmed reported cases of adverse events to isosulfan blue dye.1-7,10,11,14-33 Tables 3 and 4 provide a summary of characteristics, reactions observed, and clinical course of the patients in studies included in this review. Including the 2 patients in the present series (n=110), most patients had a grade 3 (57/110, 51.8%) reaction, followed by grade 1 (40/110, 36.4%) and grade 2 (13/110, 11.8%). Among the patients for whom hospital course was reported (n=34), 23 known patients were admitted to the SICU. Additionally, the planned surgery was canceled for 12 of 26 patients for whom these data were available, but the status of the planned procedure was unknown for 84 patients. In our series, the first patient required SICU monitoring and was discharged on the second hospital day, while the second patient had a less severe reaction, recovered more favorably, was able to complete the planned surgery, and only required overnight PACU monitoring prior to discharge.

Given the potential for complex pharmacologic interactions among antibiotics and anesthetic agents administered during surgical procedures, isolating the reaction can be difficult.15 Although the temporal relationship provides a challenge, the rate of allergic reactions to antibiotics and anesthetic agents is considered significantly smaller than the rate of allergic reactions to isosulfan blue dye. For example, cefazolin allergy has been reported in 1/17,000 (0.006%) cases compared to the reported 0.6% to 2.5% of isosulfan blue dye allergies.4,5,11 Additionally, most patients have been previously exposed to beta-lactam antibiotics.4 One patient in our series underwent outpatient allergy profile testing to rule out reactions to the antibiotics and anesthetic agents used during surgery (Table 2).

Severe allergic reactions to isosulfan blue dye can extend hospital stay, and the associated intensive care poses a significant financial and mental burden on patients. Studies have previously explored the alternatives to isosulfan blue dye, such as fluorescent dye or methylene blue; however, similar reactions have been reported.34 Skin testing prior to the procedure or preprocedural steroids or antihistamines are other options to avoid anaphylaxis in this setting, especially in high-risk patients with similar allergies or history.
| Study                        | N  | Age, years, Sex | Dose | Grade 1 | Grade 2 | Grade 3 | Time From Administration to Reaction | Surgery Canceled | Time in SICU |
|------------------------------|----|-----------------|------|---------|---------|---------|---------------------------------------|-----------------|-------------|
| Longnecker et al, 1985<sup>17</sup> | 1  | N/R             | N/R  | 1       | N/R     | 1 min   | N/R                                  | 24 h            |             |
| Leong et al, 2000<sup>18</sup>    | 3  | 38, M           | 4.8 mL | 1      | 1       | 15 min  | Yes                                   | 36 h            |             |
|                               | 66, F | 4.7 mL | 1       | 15 min  | No      | None    |                                       |                 |             |
|                               | 81, F | 4.8 mL | 1       | 15 min  | Yes     | 48 h    |                                       |                 |             |
| Lyew et al, 2000<sup>9</sup>     | 1  | 48, F           | 5 mL  | 1       | 5 min   | No      | 18 h                                  |                 |             |
| Cimmino et al, 2001<sup>11</sup> | 5  | 22, F           | 3 mL  | 1       | 10 min  | N/R     | Yes, time N/R                          |                 |             |
|                               | 72, F | 3 mL  | 1       | 8 min   | N/R     | Yes, time N/R |                                       |                 |             |
|                               | 50, F | 3 mL  | 1       | 40 min  | N/R     | N/R     |                                       |                 |             |
|                               | 47, F | 5 mL  | 1       | 30-40 min | N/R  | N/R     |                                       |                 |             |
| Albo et al, 2001<sup>4</sup>    | 7  | 75, F           | 5 mL  | 1       | 20 min  | N/R     | 48 h                                  |                 |             |
|                               | 75, F | 5 mL  | 1       | 15 min  | N/R     | 24 h    |                                       |                 |             |
|                               | 50, F | 5 mL  | 1       | 15 min  | N/R     | 24 h    |                                       |                 |             |
|                               | 47, F | 5 mL  | 1       | 15 min  | N/R     | 24 h    |                                       |                 |             |
|                               | 65, F | 5 mL  | 1       | 30 min  | N/R     | 48 h    |                                       |                 |             |
| Kuerer et al, 2001<sup>19</sup> | 1  | 75, F           | 5 mL  | 1       | 40 min  | No      | N/R                                  |                 |             |
| Krouse and Schwarz, 2001<sup>20</sup> | 1  | 63, F           | 4 mL  | 1       | N/R     | No      | N/R                                  |                 |             |
| Sadiq et al, 2001<sup>21</sup>  | 2  | 52, F           | 2 mL  | 1       | 45 min  | No      | None                                 |                 |             |
|                               | 57, F | 2 mL  | 1       | 25 min  | Yes     | None    |                                       |                 |             |
| Kuerer et al, 2001<sup>22</sup> | 1  | 52, F           | 5 mL  | 1       | N/R     | Yes     | N/R                                  |                 |             |
| Giménez et al, 2001<sup>23</sup> | 2  | 48, F           | 4 mL  | 1       | 5 min   | No      | N/R                                  |                 |             |
|                               | 60, F | 2 mL  | 1       | 5 min   | No      | None    |                                       |                 |             |
| Laurie et al, 2002<sup>10</sup> | 2  | 60, F           | 5 mL  | 1       | 5 min   | Yes     | 48 h                                  |                 |             |
|                               | 62, F | 5 mL  | 1       | 40 min  | Yes     | None    |                                       |                 |             |
| Montgomery et al, 2002<sup>24</sup> | 39 | N/R           | N/R  | 27      | 3       | 9       | 44 min (mean)                        | N/R            | N/R         |
| Efron et al, 2002<sup>24</sup>  | 1  | 54, F           | 5 mL  | 1       | 10 min  | No      | 24 h                                  |                 |             |
| Stefanutto et al, 2002<sup>25</sup> | 1  | N/R           | N/R  | 1       | N/R     | N/R     |                                       | N/R            |             |
| Sprung et al, 2003<sup>26</sup>  | 1  | 53, F           | 4 mL  | 1       | 1 min   | Yes     | N/R                                  |                 |             |
| Raut et al, 2004<sup>27</sup>   | 3  | N/R           | 5 mL  | 3       | N/R     | N/R     |                                       | N/R            |             |
| Sandhu et al, 2005<sup>6</sup>  | 1  | 45, F           | 5 mL  | 1       | 10 min  | Yes     | 48 h                                  |                 |             |
| Raut et al, 2005<sup>15</sup>   | 4  | 73, F           | 5 mL  | 1       | 105 min | N/R     | None                                 |                 |             |
|                               | 62, F | 5 mL  | 1       | 45 min  | N/R     | None    |                                       |                 |             |
|                               | 53, F | 5 mL  | 1       | 75 min  | N/R     | None    |                                       |                 |             |
|                               | 58, F | 5 mL  | 1       | 10 min  | N/R     | None    |                                       |                 |             |
| Amr et al, 2005<sup>16</sup>    | 7  | N/R           | N/R  | 6       | 1       | N/R     | N/R                                  | N/R            |             |
| Komenaka et al, 2005<sup>28</sup> | 3  | N/R           | N/R  | 3       | 23 min (mean) | N/R  | N/R                                  |                 |             |
| Saft and Sarap, 2007<sup>29</sup> | 1  | 54, F           | 5 mL  | 1       | 20 min  | Yes     | N/R                                  |                 |             |
| Kaufman et al, 2008<sup>2</sup> | 2  | 62, F           | 5 mL  | 1       | 30 min  | N/R     | 24 h                                  |                 |             |
|                               | 77, M | 1.8 mL | 1       | 1 min   | N/R     | 24 h    |                                       |                 |             |
| Liang and Carson, 2008<sup>7</sup> | 1  | 48, F           | 5 mL  | 1       | 15 min  | Yes     | 36 h                                  |                 |             |
| O’Sullivan and Morrow, 2008<sup>30</sup> | 1  | 77, F           | 8 mL  | 1       | N/A     | No      | None                                 |                 |             |
| Cinar et al, 2012<sup>31</sup>  | 1  | 65, F           | 5 mL  | 1       | 30 sec  | No      | 2 h                                   |                 |             |
Table 3. Continued

| Study                              | N  | Age, years, sex | Dose | Grade 1 | Grade 2 | Grade 3 | Time From Administration to Reaction | Surgery Canceled | Time in SICU |
|------------------------------------|----|----------------|------|---------|---------|---------|--------------------------------------|-----------------|--------------|
| Haque and Nossaman, 2012          | 2  | 83, F          | 4 mL | 1       | N/R     | No      | N/R                                  |                 |              |
| Reed et al, 2014                  | 1  | 44, F          | N/R  | 1       | 20 min  | No      | N/R                                  |                 |              |
| Ortiz et al, 2015                 | 1  | 82, F          | 1 mL | 1       | 15 min  | Yes     | 48 h                                 |                 |              |
| Wang et al, 2018                  | 12 | N/R            | N/R  | 12      | N/R     | Yes, time N/R |                      |                 |              |
| Present Study                     | 2  | 46, F          | 5 mL | 1       | 5 min   | Yes     | 18 h                                 |                 |              |
|                                   | 51 | 5 mL           |      | 1       | 25 min  | No      | None                                 |                 |              |

N/R, not reported; SICU, surgical intensive care unit.

of asthma. The benefits of these interventions should be weighed against risks or health care costs through future prospective studies.

The true incidence of isosulfan blue dye allergic reaction is likely higher than the reported 0.6% to 2.5%. Despite the range of allergic reaction—from skin changes to anaphylaxis—the literature principally reports anaphylaxis-type reactions requiring SICU level of care. Selective reporting of more severe reactions introduces selection bias as the patients with the most severe reactions who warrant higher levels of care are more likely to be reported than patients with less severe reactions. Of the studies included in this review, 19 of 29 studies reported only patients who had experienced grade 3 reactions. The true incidence of total isosulfan blue dye allergic reaction (regardless of grade) is likely higher than the cases identified in the literature would suggest; the percentage of anaphylaxis/shock grade 3 among all patients with isosulfan blue dye allergy likely remains low.

Table 4. Summary of Clinical Course of Patients Including the Present Series

| Variable                              | Value                                      |
|---------------------------------------|--------------------------------------------|
| Demographics                          |                                             |
| Total patients, n                     | 110                                        |
| Age, years, mean (range); n=44        | 58.3 (22-83)                               |
| Age not available, n (%)              | 66/110 (60)                                |
| Male, n (%)                           | 3/44 (6.8)                                 |
| Female, n (%)                         | 41/44 (93.2)                               |
| Reaction, n (%)                       |                                             |
| Grade 1—Generalized swelling, urticaria, mild rash | 40/110 (36.4)                              |
| Grade 2—Hypotension, vasopressors not given | 13/110 (11.8)                              |
| Grade 3—Hypotension, vasopressors given | 57/110 (51.8)                              |
| Dosage of isosulfan blue, mL, median (range); n=44 | 5 (1.0-8.0)                                |
| Administration to reaction time, min, mean (range); n=42 | 23.28 (0.5-105)                             |
| Surgery status, n (%); n=26           |                                             |
| Canceled                              | 12/26 (46.1)                               |
| Not canceled                          | 14/26 (53.8)                               |
| Not available                         | 84/110 (76.4)                              |
| Surgical intensive care unit admission; n=34 |      |
| Yes, n (%)                            | 23/34 (67.6)                               |
| Time in intensive care, h, mean (range) | 33.1 (2-72)                                |
| No, n (%)                             | 11/34 (32.4)                               |
| Not available, n (%)                  | 76/110 (69.1)                              |
| Death                                 | None                                       |

CONCLUSION

The use of isosulfan blue dye is a valuable technique in lymph node biopsy; however, isosulfan blue dye is associated with anaphylactic reactions and the consequences may be serious in some cases, as summarized in this review. These cases underscore the importance for operating room personnel to be familiar with such potential reactions so they can recognize and effectively treat them early in acute care settings.

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