

Correspondence and Replies

Isosulfan blue-induced perioperative systemic allergic reactions



To the Editor:

Banerji et al¹ describe the allergy assessment of 123 patients who had perioperative allergic reactions, including the experience of those who went on to have subsequent anesthesia after their allergy evaluation. The authors note that their diagnostic testing expanded over time and that they identified new causative agents. Although they mention blue dye among other new potential culprits for perioperative allergic reactions, their series identified no patients where this was the identified allergen. We have identified isosulfan blue as the agent responsible for perioperative allergic reactions in 3 patients over only the last 6 months (Table I) and suspect that this allergy may be more common than realized. All 3 patients went on to uneventful subsequent surgery with exposure to the same medications except isosulfan blue (and in one case also ondansetron).

At our institution, we follow a similar approach as that described by Banerji et al, carefully examining the anesthesia record for all medications administered before the onset of symptoms suggestive of an allergic or anaphylactic reaction and also evaluating substances to which the patient may have been exposed but that are not specifically mentioned, such as latex. However, isosulfan blue is not listed on the anesthesia record because it is not administered by the anesthesiologist. Instead, its administration is described in the operative report, because it is administered by the surgeon. For this reason, its administration

may be overlooked, and it may thus be responsible for some of the cases where no culprit allergen is identified.

The package insert for isosulfan blue states, "Case series report an overall incidence of hypersensitivity reactions in approximately 2% of patients. Life-threatening anaphylactic reactions have occurred. Manifestations include respiratory distress, shock, angioedema, urticaria, pruritus" (isosulfan blue injection, solution; Mylan Institutional LLC, Morgantown, WV). Of 2392 sequential patients who underwent sentinel lymph node mapping for breast cancer involving isosulfan blue dye at a single institution, 1.6% had a documented allergic reaction; most involved urticaria, but the incidence of hypotensive reactions was 0.5%.² A recent meta-analysis estimated the rate of anaphylaxis with all blue dyes, including isosulfan blue, patent blue, and methylene blue, to be 0.061%, noting a higher rate with breast cancer surgery (0.083%) and a higher rate with isosulfan blue (0.160%) compared with patent blue (0.05%) and methylene blue (0.0006%).³ The lower rates in the meta-analysis may be due to exclusion of case series and lower grades of anaphylaxis.

Most reactions to isosulfan blue occur on first exposure. It has been hypothesized that sensitization may occur through prior exposure to patent blue and other structurally related triaryl-methane dyes used in textiles, cosmetics, and medications.^{4,5} Cross-reactivity between isosulfan blue and patent blue has been reported.⁵ Should a patient who has had an allergic reaction to isosulfan blue require a dye in the future, methylene blue, which is not structurally related to isosulfan blue or patent blue, may be considered.³⁻⁶

In evaluating perioperative allergic reactions, we recommend careful scrutiny not only of the anesthesia record but also the

TABLE I. Patients with isosulfan blue-induced intraoperative systemic allergic reactions

Age	Sex	Type of surgery	Symptoms	Treatment for allergic reaction	Isosulfan blue skin test results (millimeter wheal/millimeter erythema)	Skin test results (millimeter wheal/millimeter erythema) for other substances given before reaction	Outcome of subsequent surgery
55	Female	Mastectomy	Flushing, hypotension (systolic 60s)	Ephedrine, phenylephrine, epinephrine, diphenhydramine	Prick 10 mg/mL (1%): 0; intradermal 1 mg/mL (0.1%): 10/35	Cefazolin, dexamethasone, fentanyl, midazolam, propofol: negative	Uneventful despite receipt of cefazolin, dexamethasone, fentanyl, midazolam, propofol
40	Female	Mastectomy	Hypotensive (50s-60s/30s, refractory to multiple doses of phenylephrine), low O ₂ saturation (80%)	Phenylephrine, diphenhydramine, methylprednisolone	Prick 10 mg/mL (1%): 5/40; intradermal: not done	Cefazolin, dexamethasone, fentanyl, metoclopramide, propofol: negative; ondansetron prick full strength 0, intradermal 1:100 9/22	Uneventful despite receipt of cefazolin, dexamethasone, fentanyl, metoclopramide, propofol
64	Female	Mastectomy	Flushing, hives	Ephedrine, phenylephrine, diphenhydramine	Prick 10 mg/mL (1%): 5/8; intradermal 1 mg/mL (0.1%): 10/15	Cefazolin, dexamethasone, fentanyl, midazolam, propofol: negative	Uneventful despite receipt of cefazolin, dexamethasone, fentanyl, midazolam, propofol

operative notes, and also consideration of isosulfan blue as a potential culprit.

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Reply to “Isosulfan blue-induced perioperative systemic allergic reactions”



To the Editor:

We thank Dr Kelso for his correspondence¹ to our article “Perioperative allergic reactions: allergy assessment and subsequent anesthesia” in the *Journal of Allergy and Clinical Immunology: In Practice*.²

Blue dyes including methylene blue, patent blue, and isosulfan blue are used clinically to identify sentinel lymph nodes in patients undergoing oncologic evaluations. A recent meta-analysis describes a 0.06% anaphylaxis rate to blue dyes, whereas another single-center study describes hypotension on 0.5% of cases using isosulfan blue dye. Overall, blue dyes are indeed being increasingly identified as “hidden” causative agents of perioperative allergic reactions,^{3,4} and allergists should include them in the list of possible causative agents when evaluating patients with perioperative allergic reactions. Allergists can also perform dye skin testing using the published nonirritating skin testing concentrations as part of the comprehensive evaluation in cases where dyes were used.^{5,6}

We agree that a thorough review of the electronic medical records including the anesthesia record and operative report is needed as part of the allergy consultation and assessment. At our academic medical center, we also review the operating room nursing record, which may document irrigations such as heparin and saline mixture, bacitracin and saline mixture, and Visipaque dye given intra-arterially. Lastly, a comprehensive approach to perioperative allergic reactions should include review of the medication administration report where

all agents given during a procedure should be thoroughly documented.

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The allergic effector unit: From basic science to drug-targetable mast cell-eosinophil interactions in patients



To the Editor:

We read with great interest Guillet et al's Clinical Communication¹ presenting the effect of mepolizumab administration in an eosinophilic bronchial asthma patient with concomitant idiopathic mast cell (MC) activation syndrome. The authors found that mepolizumab administration resulted in a reduction of blood eosinophilia, eosinophilic cationic protein (ECP), and serum tryptase levels, with amelioration of asthma, gut, and skin symptoms.¹ Interestingly, although both omalizumab and mepolizumab reduced serum tryptase, only the latter decreased asthma symptoms. This is possibly due to omalizumab binding to circulating free IgE, thus not affecting already bound IgE.²

The reduction in tryptase and ECP serum levels might be due to a direct effect of mepolizumab on MCs. It was published that administration of mepolizumab in pediatric eosinophilic esophagitis significantly reduced MC numbers and occurrence of MC-eosinophils (Eos) couples due to inhibition of IL-9 production from Eos, thus influencing MC survival in the gut.³ Mepolizumab can affect the Eos, which, when not inhibited, engage MCs in a physical and soluble crosstalk we named allergic effector unit (AEU). Indeed, in previous works, we showed that the activating receptor CD48 on human cord blood-derived MCs engages CD244/2B4 on peripheral blood Eos, resulting in activation of both cells.⁴ Importantly, MCs and Eos produce several mediators