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Adverse Reactions to Isosulfan Blue During Selective Sentinel Lymph Node Dissection in Melanoma

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Background: Selective sentinel lymph node (SLN) dissection can spare about 80% of patients with primary melanoma from radical lymph node dissection. This procedure identifies the SLN either visually by injecting isosulfan blue dye around the primary melanoma site or by handheld gamma probe after radiocolloid injection.

Methods: During selective SLN mapping, 1 to 5 ml of isosulfan blue was injected intradermally around the primary melanoma. From November 1993, to August 1998, 406 patients underwent intraoperative lymphatic mapping with the use of both isosulfan blue and radiocolloid injection. Three cases of selective SLN dissection, in which adverse reactions to isosulfan blue occurred, were reviewed.

Results: We report three cases of anaphylaxis after intradermal injection with isosulfan blue of 406 patients who underwent intraoperative lymphatic mapping by using the procedure as described above. The three cases we report vary in severity from treatable hypotension with urticaria and erythema to severe cardiovascular collapse with or without bronchospasm or urticaria.

Conclusions: In our series, the incidence of anaphylaxis to isosulfan blue was approximately 1%. Anaphylaxis can be fatal if not recognized and treated rapidly. Operating room personnel who participate in intraoperative lymphatic mapping where isosulfan blue is used must be aware of the potential consequences and be prepared to treat anaphylaxis.

Key Words: Anaphylaxis—Isosulfan blue—Melanoma—SLN.

The sentinel lymph node (SLN) is identified either by visual identification after injection of a blue dye, such as isosulfan blue,[1] around the primary melanoma site or by intraoperative gamma probe detection after radiocolloid injection.[2] Histopathological examination and identification of metastatic melanoma in the first lymph node that drains an area with melanoma (i.e., the SLN) can predict the presence of metastatic melanoma in the remainder of the associated lymphatic basin. Selective SLN dissection is a technique that identifies invasive primary melanoma and can spare as many as 80% of patients from radical lymph node dissection.[3] Overall, the success rate of harvesting the SLN by isosulfan blue alone is 82%, by radioactive mapping alone, 94%, and by using both methods, 98%.[3] Selective SLN dissection is currently being evaluated for the management of other malignancies. This method may potentially limit radical lymph node dissection in breast cancer,[4] high-risk endometrial carcinoma,[5] and Hurthle cell thyroid neoplasms.[6] Isosulfan blue is also used during intraoperative lymphatic mapping for non-small-cell lung cancer,[7] squamous cell carcinomas of the head and neck,[8] squamous cell cancer of the vulva,[9] and colon cancer.[10] As the use of this technique increases, it is important that clinicians be alert to both the potential adverse effects of isosulfan blue and the systemic manifestations of its use.

We report three cases of anaphylaxis after intradermal injection with isosulfan blue of 406 patients who underwent intraoperative lymphatic mapping by using both isosulfan blue and radiocolloid injection for melanoma. The systemic manifestations associated with the use of

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isosulfan blue during selective SLN dissection for melanoma are discussed.

PATIENTS AND METHODS

SLN Identification and Surgical Technique

Immediate preoperative lymphoscintigraphy was performed after intradermal injection of the ^{99m}Tc in sulfur colloid into the area of the melanoma biopsy site as previously described.[11] After transfer to the operating room and induction of general anesthesia, 1 to 5 ml of isosulfan blue (Lymphazurin 1%; Ben Venue Laboratories, Bedford, OH) was injected intradermally in the area of the primary melanoma. Intraoperative mapping of the SLN was achieved by using a handheld gamma probe (Neoprobe 2000, Neoprobe, Dublin, OH) and staining with blue dye. A 2- to 4-cm incision was made over the marked area of greatest activity as detected by the held probe. The incision was carried down through the subcutaneous fat, and the superficial fascia was incised. By using the gamma probe, the increased radioactivity, expressed as counts per second, was detected per orientation and dissection was carried down to the appropriate lymph node. A blue stained lymph node confirmed the findings of radioisotope activity, leading to removal of the SLN. A sentinel or "hot" lymph node was defined as any lymph node with an in vivo radioactivity count three times greater than the background or an ex vivo count 10 times greater than the background.[12] After removal of the SLN, the handheld gamma probe was used to search the resection bed to assure that there was no residual elevated radioactivity. Further exploration was performed if the resection bed count remained high.[11]

After selective SLN dissection, the wound was closed in three layers, with the deep and superficial layer each closed with interrupted 3-0 Dexon sutures (Davis & Geck, Manati, PR) and the skin closed with either running subcuticular sutures of 4-0 Dexon or skin staples. After changing gloves and instruments, the primary site was excised according to the thickness of the primary melanoma. A total of 406 patients underwent selective SLN dissection between November 21, 1993, and August 25, 1998. Three cases of anaphylaxis occurred intraoperatively. These cases are discussed below.

Case Reports

Patient 1: HS

An 81-year-old female was admitted July 1, 1997, after excision of a left upper arm melanoma (Breslow thickness, 2.2 mm; Clark level IV). Medical history was remarkable for hypertension and hypothyroidism. She had no known drug allergies. Her daily medications consisted of quinapril, Premarin, and Levoxyl. On physical examination, she was noted to have a Mallinpati 3 airway, normal heart, and lung examination.

After radiocolloid injection and lymphoscintigraphy, she was transferred to the operating room for a wide re-excision of the left upper arm melanoma and a left axillary selective SLN dissection. After induction of anesthesia with fentanyl (50 μg) and propofol (150 mg), a laryngeal mask airway (Brain Medical Ltd, Berkshire, UK) was placed without adverse reaction. Anesthesia was maintained with propofol 100 μg/kg/min, and oxygen and nitrous oxide levels were maintained at 33% and 66%, respectively. Isosulfan blue (4.8 ml) was injected intradermally at the site of the left upper arm melanoma excision and cefazolin (1 g) administered intravenously. Approximately 15 minutes after the injection of isosulfan blue and administration of cefazolin, the systolic blood pressure declined from 115 to 70 mm Hg and was unresponsive to a bolus of Neo-Synephrine (500 μg) or ephedrine (20 mg), with the blood pressure declining to 50/20 mm Hg. Neither bronchospasm nor urticaria were noted. The anesthetics were discontinued, oxygen was increased to 100%, the laryngeal mask airway removed, and the trachea intubated with the aid of suxamethonium (100 mg). The patient was successfully resuscitated with epinephrine and crystalloid (5 liters) and given methylprednisolone (125 mg). The patient was stable when transferred to the intensive care unit for monitoring and to rule out myocardial infarction. Her postoperative course was unremarkable and there was no evidence of a myocardial infarction. The surgery was completed successfully 2 days later, without any adverse sequelae, under local anesthesia with monitored anesthesia care. For the second procedure, the patient underwent radiocolloid injection and lymphoscintigraphy and was then premedicated with Versed (1.5 mg) and transferred to the operating room. Intraoperatively, she received fentanyl (250 μg). The procedure was uneventful.

Patient 2: MH

A 38-year-old male was admitted on August 5, 1998, after a left posterior shoulder lesion biopsy showing superficial spreading malignant melanoma (Breslow thickness, 2.2 mm). Past medical history included asthmatic bronchitis, treated over the previous 1 year with metered dose inhalers (Combivent and Flovent), and ulcerative colitis in remission since 1992. He was allergic to erythromycin and was taking no other medicines. Physical examination revealed a Mallinpati class 2 airway, supple neck, normal heart, and lung examination.

After radiocolloid injection and lymphoscintigraphy, the patient was premedicated with midazolam (2 mg) and transferred to the operating room for wide excision of the left scapular melanoma and left selective axillary SLN biopsy. After induction with fentanyl titrated to 200 μg, propofol (200 mg), and rocuronium (50 mg), the patient was easily intubated and anesthesia was maintained with sevoflurane. Oxygen and nitrous oxide levels were maintained at 40% and 60%, respectively. Bilateral breath sounds were equal and without wheezing. Cefazolin (1 g) was administered 10 minutes after induction. The patient was placed in the right lateral position and isosulfan blue (4.8 ml) injected intradermally in the area of the previously excised melanoma. Re-excision preceded the left axillary selective SLN dissection. Thirty minutes after injection of the dye, the systolic blood pressure decreased from 140/82 to 40/20 mm Hg, heart rate increased to 100 beats per minute, and pulse oximetry oxygen saturation decreased from 100% to 97%. The inhaled sevoflurane concentration was decreased and the patient was treated with a bolus of ephedrine (5 mg) and Neo-Synephrine (200 μg) without a significant response. The patient was noted to have bilateral wheezing, increased peak pressures, and truncal urticaria. Anesthetics were discontinued. The patient was then treated with epinephrine (0.4 mg) and an epinephrine infusion of 30 μg/min was started. Initially, additional epinephrine boluses of 0.1 to 0.2 mg were also required to maintain systolic pressures at greater than 100 mm Hg. After acquisition of large-bore intravenous access, fluid resuscitation with crystalloid (6700 ml), 5% albumin (1000 ml), and Hespan (500 ml) was required to maintain systolic pressures above 100 mm Hg. Hydrocortisone (100 mg) and Benadryl (50 mg) were given intravenously. SLN dissection was canceled and the patient was transferred to the intensive care unit and required continued volume and vasopressor support to maintain systolic blood pressure above 100 mm Hg. Ventricular ectopy was noted and initially was successfully treated with a bolus of Lidocaine (100 mg). Atrial fibrillation at a rate of 140 beats per minute developed. Direct current cardioversion was performed three times without success. With time, the patient stabilized, and atrial fibrillation resolved as did the bronchospasm and urticaria. Vasopressor and fluid support were gradually withdrawn during the subsequent 24 hours. The patient was transferred back to his room 36 hours later and was discharged home on hospital day 3. The patient had no recollection of the above events and returned for subsequent selective SLN dissection, 28 days later, without any adverse sequelae, under local anesthesia with monitored anesthesia care. During that procedure, after radiocolloid injection and lymphoscintigraphy, the patient was premedicated with Versed (2 mg) and transferred to the operating room. During the procedure, he received propofol (60 μg/kg/min) supplemented with fentanyl (75 μg) intravenously.

Patient 3: JC

A 66-year-old female was admitted August 25, 1998, with the diagnosis of left arm nodular melanoma (Breslow thickness, 1.2 mm; Clark's level III). Past medical history was unremarkable. She had no allergies and was taking no medicines. On physical examination, a Mallinpati 1 airway was noted and examination of the heart and lungs was within normal limits.

After radiocolloid injection and lymphoscintigraphy, the patient was premedicated with midazolam (0.5 mg) and transferred to the operating room for wide excision of the left upper arm melanoma and selective SLN dissection of the left axilla. After induction with propofol (50 mg) and uneventful placement of a laryngeal mask airway (Brain Medical Ltd) no. 3, anesthesia was maintained with propofol (100 μg/kg/min), with oxygen and nitrous oxide levels maintained at 31% and 69%, respectively, and fentanyl titrated to 200 μg over the course of the operation. Isosulfan blue (4.7 ml) was injected intradermally at the site of the left arm melanoma. No antibiotics were given. Fifteen minutes after the isosulfan blue injection, the systolic blood pressure decreased from 110 to 80 mm Hg and the patient was treated with a bolus of ephedrine (25 mg), which initially maintained systolic pressures at greater than 100 mm Hg. Further hypotension, with systolic pressure as low as 55 mm Hg, was responsive to crystalloid (2400 ml) and Neo-Synephrine to a total of 10 mg during the subsequent 45 minutes. Oxygen saturation by pulse oximetry decreased from 98% to 94% within 15 minutes but returned to 100% by the end of the case. Twenty-five minutes after injection of isosulfan blue, truncal urticaria and erythema were noted and Benadryl (50 mg) was given intravenously. After completion of the surgery, the patient was transferred to a recovery room, kept well hydrated, and observed. Postoperatively, the patient was stable, the urticaria had resolved, and the patient was discharged to home the next day.

DISCUSSION

Anaphylaxis during anesthesia is often a clinical diagnosis presenting, in decreasing frequency, with cardiovascular collapse, erythema, angioedema, bronchospasm (severe or transient), urticaria and/or rash, gastrointestinal symptoms, and pulmonary edema.[13] Cardiovascular

collapse without other clinical signs or symptoms occurs in 10% of the reported cases of anaphylaxis.[14]

Both anaphylactic and anaphylactoid reactions may present with similar findings, because both are the result of massive mast cell histamine release. However, the mechanism of the reactions differs. Anaphylaxis is the result of covalent binding of IgE drug-specific antibody to mast cells with subsequent release of intracellular contents. The reaction may be self-perpetuating. Anaphylactoid reactions are also the result of mast cell histamine release but are dose related rather than self-perpetuating. They are not IgE antibody dependent. Rapid release of these mediators in large quantities is responsible for the mucosal edema and capillary leakage that can lead to fatal shock and asphyxia.[15]

The three cases we report vary in severity from treatable hypotension with urticaria and erythema to severe cardiovascular collapse with or without bronchospasm or urticaria. Previous reports of anaphylaxis support this observed spectrum of clinical response among patients. During anesthesia, anaphylaxis develops 90% of the time within 10 minutes after intravenous administration of the causal agent.[16] The time delay of 15 to 30 minutes observed in our cases most likely reflects intradermal introduction of antigen rather than intravenous administration of an anesthetic agent.

The onset of a drug reaction should be suspected when there is an acute heart rate increase of more than 30 beats per minute or the systolic blood pressure decreases by more than 30 mm Hg. At this point, anesthetics should be discontinued. The patient should be treated with 100% oxygen, and intravenous fluids should be increased. Often more than 5 to 6 liters of crystalloid may be required, which necessitates prompt attainment of appropriate venous access. Persistent tachycardia and low systemic vascular resistance should be treated with 0.2 to 0.4 mg of intravenous epinephrine. A 5- to 10-μg-per-minute epinephrine infusion may be needed to maintain hemodynamic stability. Intravenous antihistamines (H1 and H2 blockers) to alter permeability and systemic hemodynamics should be considered if the reaction persists.[15–18]

Determination that an episode of anaphylaxis has resolved should be made with caution because the reaction may be biphasic. A delayed reaction may occur hours after the exposure to antigen. Tachycardia should not be treated with β-blockers and patients taking β-blockers may be refractory to treatment. Cardiovascular changes caused by histamine normally result in release of epinephrine from the adrenal glands.[16,18] In the presence of β-blockade, absence of β-stimulation limits the compensatory response.

It is often difficult to determine the causative agent of anaphylaxis under general anesthesia, in the absence of confirmatory testing, which was unavailable to us. Anaphylaxis is estimated to occur at a rate of 1 in 6000 general anesthetics. Neuromuscular blocking agents cause 59% of cases, with suxamethonium comprising 39% of the reactions caused by muscle relaxants. Hypnotics, such as thiopentone or propofol (less frequently), comprise a minority of anaphylactic reactions (7%), as is the case for narcotics (2.3%).[19] In our cases, the temporal relationship between the injection of isosulfan blue and the clinical response make this agent the most probable cause.

Two of the three patients reported here were treated with cefazolin as well as injected with isosulfan blue. Cefazolin is a reported but rare cause of anaphylaxis. In Japan, the incidence of anaphylactic shock caused by cefazolin is reported as 1 in 16,960.[20] In the United States, the rate is unknown because of underreporting, but it is thought to occur less frequently than anaphylaxis caused by penicillin (1–5/10,000). Adverse reactions to cephalosporins have decreased since the first-generation cephalosporins were introduced, because early drug contamination with penicillin has been reduced.[21] We have reviewed our records from January 1998 to November 1999 for the use of perioperative antibiotics. Of 11,323 patients who underwent either general anesthesia or monitored anesthesia care, 7,641 received antibiotic therapy. Most of our patients receive cefazolin. All three instances of intraoperative anaphylaxis have occurred in patients injected with isosulfan blue. If either of the two cases reported here were caused by cefazolin, we would expect to have seen other cases in our surgical population. In addition, adverse reactions to cephalosporins are thought to occur most frequently in patients who are known to be allergic to penicillin, because one-half or more of patients report penicillin allergy.[21–23] None of our three patients reported allergy to penicillin.

The following are the three methods reported in the literature that may be used to confirm the diagnosis of anaphylaxis: (1) biochemical evidence of mast cell histamine release (plasma histamine, serum/plasma tryptase, or urine methyhistamine), (2) radioimmunoassay or enzyme-linked immunoassay for drug-specific IgE serum antibody, and (3) skin-prick testing of the patient with the suspect agent(s).[19,24,25] To accurately measure plasma histamine levels, the patient specimen must be collected within 15 to 60 minutes of the event and stored on ice. Serum or plasma tryptase levels and urine methyhistamine specimens required collection within 3 hours of the event. Radioimmunoassay or enzyme-linked immunoassay antibody testing is not avail-

able for all drugs and is not always positive when serum tryptase levels are elevated and skin testing is reactive.[19] A skin-prick test allows either definite or probable identification of the causative agent in approximately 75% of cases.[25]

Isosulfan blue is a rosaniline dye of the triphenylmethane type and is the only dye of this type approved for visualization of lymphatics by the Food and Drug Administration in the United States. Isosulfan blue is the 2,5-disulfonated isomer of patent blue. Patent blue has been used for a longer period of time than isosulfan blue for lymphography. It is also used more frequently than isosulfan blue for SLN identification outside the United States. Patent blue (alphazurine 2G) has long been reported to cause adverse patient reactions varying from mild allergic reactions, such as hives, to angioneurotic edema with or without laryngospasm, to anaphylaxis with cardiovascular collapse.[26–29] The frequency of these adverse reactions is unknown but estimated to be in the range of 0.6% to 2.5%. It is not known whether allergic reactions to patent blue are anaphylactic or anaphylactoid, because IgE-specific antibodies have not been identified. Previous sensitization to patent blue and other triphenylmethane dyes is thought to occur after contact with dyes used in industry to color textiles, cosmetics, detergents, paint, and inks. It is not surprising to find adverse reactions to isosulfan blue, such as we report, to be similar in type and frequency to the reactions ascribed to patent blue.

Before this report, there had been one report of anaphylaxis after injection of isosulfan blue (1.5 ml) for lymphography in a woman with squamous cell carcinoma of the cervix.[30] The other reported adverse reactions to isosulfan blue are mild allergic reactions. Allergic reactions with localized swelling at the site of administration and mild pruritis of the hands, abdomen, and neck are described with a frequency of 1.5% (package insert). Adverse reactions to isosulfan blue are thought to be infrequent, because no serious reactions occurred in 543 adults during phase III clinical trials of isosulfan blue 1%.[31] In our series, the frequency of severe anaphylactic reactions is 1%, with three cases in 406 patients injected with isosulfan blue.

There are several other systemic manifestations that may be noted after intradermal injection with isosulfan blue. Acute transient or a more prolonged decline in oxygen saturation, as measured by pulse oximetry, may be observed.[32] We have noted the oxygen saturation by pulse oximetry to frequently decrease 1% to 2% after injection with isosulfan blue. This modest degree of apparent desaturation by pulse oximetry may be prolonged, often lasting until the end of the case. The decrement in the measured oxygen saturation is expected because maximal absorption for isosulfan blue occurs at 647 nm. The maximal absorption of deoxyhemoglobin occurs at 660 nm. The absorption of isosulfan near the absorption of deoxyhemoglobin artificially increases the measured amount of unsaturated oxygen, which, in turn, decreases the reported percent oxygen saturation. This artificial decrease in the observed oxygen saturation also occurs with patent blue.[33,34]

After intradermal injection with isosulfan blue, some patients appear cyanotic, because the dye drains from the lymphatics into the venous system and circulates through capillary beds. Although it is important to assure that oxygen saturation is adequate, it is also advisable to alert residents, postoperative recovery personnel, and the patient of this occurrence.

Patients should be informed of these changes, which they may not observe until hours after the procedure and may be a cause of concern if unexpected. Ten percent of the dye is excreted unchanged in the urine, which results in blue urine for the first 24–48 hours. Last, the injection site may stain with dye and result in a blue discoloration of the skin for up to 1 year.[35]

Although the frequency of anaphylaxis to isosulfan blue is low, anaphylaxis can be fatal if not recognized and treated rapidly. Operating room personnel who participate in intraoperative lymphatic mapping for selective SLN dissection in which isosulfan blue is injected must be aware of the potential consequences of isosulfan blue injection and be prepared to treat anaphylaxis.

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