Anaphylaxis after Peritumoral Injection of Sulphan blue 1% for Identification of the Sentinel Node in Lymphatic Mapping of the Breast: Case Report

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INTRODUCTION

Intraoperative lymphatic mapping and selective lymphadenectomy is a relatively new procedure used in many hospitals around the world to treat intermediate thickness melanoma. The technique depends on the concept of the sentinel node, which is defined as the first lymph node in a regional lymphatic basin that receives lymph flow from a primary tumour (1). In 1992, Morton et al. used a blue dye to identify the sentinel lymph node (8), and hypothesised that the absence of metastatic melanoma in that node accurately reflected the state of the remaining lymph nodes. Several studies have since been done or are in progress to assess adequacy of selective lymphadenectomy in other neoplasms, such as breast carcinoma (6).

Two techniques have been proposed and are being used to visualise the sentinel node: a vital blue dye is injected intradermally around the tumour or the scar in the case of melanomas, and peritumorally in breast cancer, which subsequently allows identification of the draining lymphatic channel and first node (sentinel node); and injection of a radiocolloid and detection of radiation with a hand-held gamma probe. Currently most authors use both techniques to increase the sensitivity of the investigation (3), although there is a tendency to rely more on the gamma probe because it is a straightforward procedure and the training period for the surgeon is shorter and easier.

In our hospital (Instituto Valenciano de Oncología) we use the technique of selective lymphadenectomy in melanoma and breast cancer. In the latter, sentinel node identification follows a protocol to assess the efficacy of the technique in this neoplasm, and is always followed by conventional axillary lymphadenectomy. Sixty-five patients with melanoma and 80 with breast cancer had had selective lymphadenectomy up to January 2000.

Sulphan blue 1% (Lymphazurin®, Ben Venue Labs, Inc, Bedford, OH 44146, USA) is used in breast cancer, and the mean dose was 3 ml (range 3–5 ml). We report two cases of anaphylactic reactions after peritumoral injection of sulphan blue for detection of sentinel nodes in two patients with breast cancer.

CASE REPORTS

Case 1

A 48-year-old woman with bilateral ductal carcinoma of the breast was scheduled for bilateral lumpectomy and axillary lymphadenectomy. Unfiltered ^{99m}Tc sulphur colloid was injected around the tumours 18 hours preoperatively. Antibiotic prophylaxis and sedation were given immediately before the operation with intravenous ceftriaxone 2 g and midazolam 3 mg. Twenty minutes before the operation, 1% sulphan blue 2 ml was injected around the tumour in each breast. Anaesthesia was induced with fentanyl hydrochloride, propofol, and rocuronium, and it was maintained with oxygen, nitrous oxide, and isofluorane.

Within five minutes the patient developed tachycardia, hypotension, facial pallor, and a generalised rash mainly on the extremities, but no bronchospasm. Arterial pressure diminished until it could not be measured with either the monitor or manual sphygmomanometer; and heart rate increased to 145 bpm.

A presumptive diagnosis of anaphylactic shock was made and treatment with volume replacement (crystalloids and colloids), corticosteroids, and anthihista-

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mines was given. As the blue dye was suspected as being responsible for the anaphylaxis, bilateral lumpectomy was done rapidly to remove it. Ten minutes later, her haemodynamic condition improved (arterial pressure: 80/40; heart rate: 110 bpm), and bicarbonate was given because arterial gas measurements showed metabolic acidosis. When the arterial pressure reached normal values, frusemide was started to remove any residue of sulphan blue. She recovered without incident and was discharged 48 hours later.

Case 2

A 60-year-old woman with an infiltrating ductal carcinoma of the breast was listed for wide excision and dissection of the sentinel node followed by conventional axillary dissection. She had previously been operated on on two occasions under general anaesthesia without any complication.

Preoperative lymphoscintigraphy, antibiotic prophylaxis, induction of anaesthesia, and injection of sulphan blue around the tumour were the same as in the previous patient. Five minutes later, the patient developed a rash with weals covering her entire body, pallor, and a drop in blood pressure. There was no evidence of bronchospasm. Treatment with corticosteroids and antihistamines was initiated, and lumpectomy was done immediately. The patient recovered her haemodynamic state in the next few minutes, and frusemide was given to eliminate the dye. Axillary lymphadenectomy was done and the patient was extubated without any further complication apart from persistence of the rash, which resolved during the following day.

ALLERGOLOGICAL STUDY

In both cases the allergological evaluation disclosed the following results: no reactions to skin tests with latex, thiopentone, propofol, fentanyl, suxamethonium, rocuronium, atropine, midazolam, or β-lactam antibiotics including cephalosporins; and reactions to skin tests with sulphan blue (Table I).

Table I. *Skin tests for sulphan blue*

Case No.	Skin prick test Sulphan blue 1%	Intradermal tests 1/1000	Intradermal tests 1/100
1	No reaction	No reaction	Reaction
2	Reaction	Reaction	Not done

Reaction: Weal equal to or larger than histamine 10 mg/ml for skin prick tests and histamine 0.1 mg/ml for intradermal tests. The tests were controlled in 10 healthy subjects with no reaction in all cases.

The diagnosis of anaphylactic reaction to sulphan blue was established, and patients were given instructions to avoid contact with this dye and related substances. On retrospective interview, no source of sensitisation was identified in the first patient. The second one mentioned exposure to different dyes and solvents in the past when she had worked painting pottery, although she did not recall any allergic reaction at that time.

DISCUSSION

Since the 1930s various dyes have been used for visualising lymph vessels before bipedal lymphography. Sulphan blue is a 2, 5 disulfonated isomer of the patent blue dye, and is structurally related to other triphenylmethane compounds. Lymphazurin® (sulphan blue 1%) is presented in a sterile aqueous solution for intradermal, subcutaneous, or peritumoral injection. Each millilitre of solution contains 10 mg sulphan blue and a phosphate buffer in sufficient quantity to yield a final pH of 6.8–7.4. It was studied in a manufacturer-sponsored clinical trial and received a favourable safety evaluation by the Food and Drug Administration (4). No reports of life-threatening toxicity associated with it were reported in another study with 659 consecutive lymphograms in children (2).

Sulphan blue has no known pharmacological action, but after its injection it is selectively picked up by the lymphatic vessels which become delineated by a bright blue colour that makes them discernible from the surrounding tissue. For this reason, it is used as an adjunct to lymphangiography to visualise the lymphatic system draining the region of injection.

Patent blue is a related dye of the triphenylmethane family that has also been widely used for the visualisation of lymphatic vessels before lymphography. Numerous cases of adverse reactions to patent blue have been described, ranging from mild itchy urticaria-like reactions to severe anaphylactic shocks. One recent report describes a case of anaphylactic shock after peritumoral injection of patent blue for sentinel lymph node biopsy in a patient with melanoma (10). In several instances of hypersensitivity to this dye, positive reactions to skin prick tests or intracutaneous tests with several concentrations of patent blue have illustrated the immunological nature of these reactions (9, 10). Nevertheless, we know of only one case of anaphylaxis after subcutaneous injection of sulphan blue reported in English (7), and although the clinical findings were highly suggestive, no allergological study was done.

The mechanism underlying the reaction to sulphan blue has not been completely elucidated. A massive and direct release of histamine from mast cells and

basophils or the activation of the alternative complement pathway, similar to what has been invoked with radiocontrast media, has also been suggested in this context (7). Alternatively, immunologically IgE-mediated reactions require a history of previous exposure to this or similar compounds of the triphenylmethane group. The latter is the most likely explanation for many of the reactions to patent blue, and is also the mechanism that seems to be implicated in our patients, because both of them reacted to skin tests, and a source of sensitisation could be identified in case 2. Unnoticed exposure to patent blue and related triphenylmethane dyes is possible because these substances are commonly used as antibacterial and antifungal agents and also in several industries such as textiles, paper, and cosmetics.

In a prospective study, Kalimo et al. found that when patent blue dye injection for lymphography was restricted to those patients who did not react to a skin-prick test (5), the incidence of clinical hypersensitivity reactions was lower than when patients were not selected on the basis of a previous skin test (0.5% compared with 2.2%). With regard to sulphan blue, the value of skin tests to predict the risk of hypersensitivity reactions must be established. One of our patients did not react to a skin prick test with sulphan blue 1%, whereas both reacted to intradermal tests.

Although controversy remains about the exact role of sentinel node biopsy in patients with early breast cancer, most recent studies favour the use of blue dye and radioisotope scan to maximise the yield and accuracy of successful localisation (4). Surgeons must therefore be aware of the possible complications of sulphan blue dye. Because these reactions can be life-threatening, emergency drugs and staff must be available, and the dye always injected when the patient is already in the operating theatre.

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