Unexpected outcome (positive or negative) including adverse drug reactions

Adverse reaction; patent blue turning patient blue

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Summary

The authors report a severe anaphylactic reaction to Patent Blue V dye used in sentinel node biopsy for lymphatic mapping during breast cancer surgery to stage the axilla. Patent Blue dye is the most widely used in the UK; however, adverse reactions have been reported with the blue dye previously. This case highlights that reactions may not always be immediately evident and to be vigilant in all patients that have undergone procedures using blue dye. If the patients are not responding appropriately particularly during an anaesthetic, one must always think of a possible adverse reaction to the dye. All surgical patients should give consent for adverse reactions to patent blue dye preoperatively. Alternative agents such as methylene blue are considered.

BACKGROUND

Patent Blue V sodium salt dye is the most widely used dye in the UK to identify the sentinel lymph node in breast cancer. Authors have reported adverse effects ranging from skin reactions to anaphylaxis. A bluish discolouration of the skin after injection is common and usually disappears following 24–48 h. Some reactions may not always present immediately. If the patients are not responding appropriately, particularly during an anaesthetic, one must always think of a possible adverse reaction to the dye. Prompt treatment is needed for those patients with anaphylaxis.

CASE PRESENTATION

A 68-year-old lady presented via the breast screening unit with a 9 mm ill-defined opacity in the left outer quadrant of her breast on mammography. She had a medical history of paroxysmal palpitations, hypertension and gastro-oesophageal reflux disease. A previous anaesthetic, while she had a hysteroscopy 3 years ago, was uneventful. On clinical examination, no palpable lesion was felt. An ultrasound of the breast showed a 6 mm hypoechoic mass, consistent with the lesion. An ultrasound core biopsy showed a grade 2 invasive ductal carcinoma. At the nuclear medicine department, preoperatively she was given 20 Mbq technetium nanocolloid and scanned 10 min afterwards so that the sentinel node could be marked. In the operation theatre, the operating surgeon injected 2 ml Patent Blue V in a subdermal fashion into the right upper outer quadrant of the breast (distant from the primary tumour which was located in the lower quadrant of the breast). She underwent a wire-guided wide local excision and axillary sentinel node biopsy. During the procedure, approximately 15 min after the dye was given, the patient's blood pressure dropped from 120 to 60 systolic and she started mounting a tachycardia. Her oxygen saturations remained constant throughout the procedure at 98%. The anaesthetist was unsure exactly why the patient was behaving in this way. Initially, the sympathomimetic amine ephedrine was given to treat the

hypotension thought to be associated with anaesthesia. It was not until after the procedure when the surgical drapes were removed that the patient was noticed to have a distinct blue discolouration with an associated urticarial rash. Her entire body was affected from earlobes, breast, arms, abdomen and legs. She was also oedematous, most noticeably in the face and arms. She had experienced an allergic reaction to the dye.

TREATMENT

Adrenaline 0.5 mg intramuscular, hydrocortisone 100 mg intravenous and chlorpheniramine were administered immediately once the reaction was diagnosed. The patient was closely monitored and also assessed by the intensive care team. She had a urinary catheter inserted for strict fluid balance measurements.

OUTCOME AND FOLLOW-UP

Postoperatively, she made a good recovery and was discharged home the next day.

DISCUSSION

Patent Blue V dye is most widely used in the UK to identify the sentinel lymph node (SLN) in breast cancer; iso-sulfan blue (from which Patent Blue V is derived) is the agent most commonly used worldwide. Surgery utilising dye is a valuable tool for breast surgeons. The American Society of Clinical Oncology suggests that blue dye with radioisotope mapping as a combined strategy produces the best rate of successful SLN mapping.¹ Varghese *et al*² describe that, by safely injecting the dye in the subdermal plane in the subareolar region, there is a 97.6% SLN identification rate.

Several authors have reported reactions ranging from skin reactions to anaphylaxis, although reported incidence rates of these reactions vary. This patient is thought to have had an anaphylactic reaction to the dye as she developed severe hypotension requiring support and required a monitored bed postoperatively. A large study of 7917 patients found an allergic reaction to the Patent Blue V dye

in only 72 patients (0.9%). Of these, 5 patients (0.06%) had similar allergic reactions to this case.³ A MEDLINE and EMBASE search for anaphylactic reactions to both isosulfan blue dye and Patent Blue dye found the reported incidence varying from 0.07% to 2.7%.⁴ Continued reports of incidence rates of adverse reactions from centres using Patent Blue V dye will be useful in refining this (figure 1) and evaluating the benefits of using alternative techniques.

Some reports in the literature suggest approaches which minimise the risk of developing blue dye reactions. Lucas *et al*⁵ reported a 0.25% rate of anaphylactic shock (grade III) with Patent Blue V dye, and recommend an alternative approach using dye injection only in cases of radioisotope detection failure. However, as only four patients were included in this series, this may not be a valid conclusion and further investigation into this approach is warranted. Another alternative strategy using preoperative prophylaxis with corticosteroids and histamine antagonists has been reported to reduce the severity of reactions to isosulfan blue dye when they occur, but not the incidence of these reactions.⁶

The current literature also suggests possible alternatives to the use of Patent Blue dye. There is antibody cross-reactivity between Isosulfan Blue and Patent Blue but not methylene blue, and it may be used as an alternative in cases of hypersensitivity.⁷ Methylene blue is thought to have lower risks of anaphylactic response.^{8–9} However, others have shown methylene blue is associated with a risk of severe necrosis and infection.¹⁰

SNL is used not only in patients with breast cancer but can be utilised in other anatomical areas such as skin oncology. SNL is considered to be both sensitive and specific in the detection of micro metastatic melanoma in regional lymph nodes. Even those patients with very small (<0.1 mm) deposits of melanoma in SLNs may be associated with adverse clinical outcomes compared with those that are SLN-negative.¹¹ A recent prospective study of 74 patients with 1-year follow-up showed that SLN-positive stage III melanoma patients have a significant risk of early recurrence.¹²

Figure 1 Patient's breast and axillary incision with blue dye reaction.

We wanted to highlight, that although Patent Blue V dye is a powerful surgical tool, adverse reactions do occur and these can vary from mild to severe. All patients undergoing dye should give consent for adverse reactions. Although alternative agents are considered, these often have similar adverse reactions. If a patient is not responding appropriately during a procedure involving the use of dye, one must always have a high index of suspicion of an allergic reaction. Early recognition of the reaction and prompt treatment is the key to a successful outcome.

Learning points

- ▶ All patients should give consent for possible adverse reactions to Patent Blue V dye.
- ▶ Anaphylactic reactions to Patent Blue V dye may vary from mild to severe.
- ▶ Severe anaphylactic reactions to Patent Blue V dye are rare.
- ▶ If the patient is not responding appropriately during a procedure involving the use of dye, one must always have a high index of suspicion of an adverse reaction.
- ▶ Early recognition of the reaction and prompt treatment is the key to a successful outcome.

Competing interests None.

Patient consent Obtained.

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