

Blue dyes in medicine – a confusing terminology

Dear Sir,

Lymphatic mapping and sentinel lymph node biopsy with blue dyes are routinely used for staging of patients with breast cancer and other malignant tumours. With increasing use of this technique, studies and reports of adverse effects have become more frequent, most commonly regarding anaphylactic reactions to the dyes used for lymphatic mapping.

Although it is very important to raise awareness and collect data of adverse events, many recent publications, among them also the latest on this topic in this journal (1), suffer from some inaccuracies that are in part due to complicated systematics of the dyes and a misleading terminology even in the chemical literature (2).

As the authors correctly state, there is a strong cross-reactivity between Patent Blue V (calcium-chelated dimer: CAS number: 3536-49-0) and Isosulfan Blue (CAS number: 68238-36-8). Both belong to the group of triarylmethan dyes and basically share the same formula; however, Patent Blue V has an additional hydroxyl group at position 5. Isosulfan Blue is the structural isomer of Patent Blue VF (CAS number: 129-17-9, not Patent Blue V) (2) (Fig. 1). Patent Blue V, not Patent Blue VF, is also used as food colourant with the number E 131 and is still on the market as such, in contrast to several reports (1, 3) (Table 1).

Methylene blue [CAS number: 61-73-4 (anhydrous methylene blue), CAS number: 7220-79-3 (methylene blue trihydrate)] is sometimes mentioned as another dye successfully used for lymphatic mapping (1, 4, 5). It is also approved for oral or intravenous administration for the treatment of methemoglobinaemia and haemolysis, but maximal doses should be respected because of its systemic toxicity. If used locally, it should be deeply injected, since it may cause severe necrosis upon intradermal administration (6). According to Tsopelas and Sutton (7), however, methylene blue does not bind to plasma proteins, having no sulfonic acid groups, and is therefore not taken up by lymph but diffuses directly into blood capillaries, which may limit its use as agent for lymphatic mapping.

An immunoglobulin E (IgE)-mediated mechanism was recently demonstrated by Woehrl et al. (8) in patients with prior anaphylactic reactions to Isosulfan Blue, although previous publications suggested pseudoallergic mechanisms. Determination of specific IgE to both dyes may be attempted by the commercial ImmunoCAP method (Pharmacia Diagnostics, Uppsala, Sweden). Given the relatively small molecular weight of Isosulfan Blue and Patent Blue V, these dyes are very likely to act as haptens. This may influence the sensitivity of *in vitro* tests, which are based on detection of complete antigens.

It is important to publish reports on adverse events from a technique with widespread use. However, a strong emphasis should be put on the correct terminology to avoid misleading or even dangerous statements. Therefore, we strongly recommend the use of CAS or CI numbers (9) to unambiguously identify the dyes.

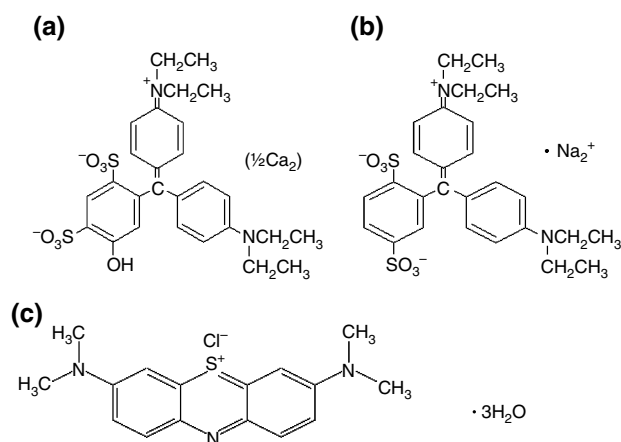


Fig. 1. Chemical formulas of Patent Blue V (A), Isosulfan Blue (B) and methylene blue (C).

Kathrin Scherer and Andreas J. Bircher
Allergy Unit, Department of Dermatology,
University Hospital Basel, Basel,
Switzerland
Verena Figueiredo
Institute of Hospital Pharmacy, University
Hospital Basel, Basel,
Switzerland

Table 1. Names and synonyms of blue dyes

Dye	Synonyms	CAS number	Colour index number	Trade names	Use
Isosulfan Blue	Patent Blue violet	68238-36-8	–	Lymphazurine	Sentinel lymph node mapping Lymphography
Patent Blue V	E131 Acid blue 3 Disulfine blue	3536-49-0	42051	Patent Blue V Guerbet	Sentinel lymph node mapping Lymphography Food and cosmetics colouring
Patent Blue VF	Acid blue 1 Food blue 3 Patent violet Alphazurine 2G	129-17-9	42045	–	Vital dye Cosmetics colouring
Patent Blue A	Acid blue 7 Alphazurine A	3486-30-4	42080	–	Cosmetics colouring
Methylene blue	Methylthioninium chloride Basic blue 9 Aniline violet	61-73-4	52015	Urolene Blue Methylene Blue Vitis	Methemoglobinaemia Vital tissue identification Antiseptic

References

1. Van Zuuren E, Poldermann M C A, Kuijken I. Anaphylaxis to Patent Blue during sentinel lymph node identification. *Contact Dermatitis* 2005; 53: 171.
2. Scherer K, Studer W, Figueiredo V, Bircher A J. Anaphylaxis to Isosulfan Blue and cross-reactivity to Patent Blue V. Case report and review of the nomenclature of vital blue dyes. *Ann Allergy Asthma Immunol* 2006 (in press).
3. Quilquini A, Hogendijk S, Hauser C. Anaphylaxis to Patent Blue. *Dermatology* 1998; 197: 400.
4. Nour A. Efficacy of methylene blue dye in localization of sentinel lymph node in breast cancer patients. *Breast J* 2004; 10: 388–391.
5. Vargas H I. Blue Dye of choice for lymphatic mapping. *J Clin Oncol* 2005; 23: 3648 [author reply 3648-9].
6. Stradling B, Aranha G, Gabram S et al. Adverse skin lesions after methylene blue injections for sentinel lymph node localization. *Am J Surg* 2002; 184: 350–352.
7. Tsopelas C, Sutton R. Why certain dyes are useful for localizing the sentinel lymph node. *J Nucl Med* 2002; 43: 1377–1382.
8. Woehrl S, Focke M, Hinterhuber G et al. Near fatal anaphylaxis to Patent Blue V. *Br J Dermatol* 2004; 150: 1037–1038.
9. Tsopelas C. Correction for Tsopelas and Sutton, *J Nucl Med* 43 (10) 1377–82. *J Nucl Med* 2002; 44: 649.

Address:

Andreas J. Bircher, MD
Allergy Unit, Department of Dermatology
Petersgraben 4, CH-4031 Basel
Switzerland
Tel: +41 61 265 4359
Fax: +41 61 265 4885
e-mail: abircher@uhbs.ch