

Anaphylactic reaction after methylene blue-treated plasma transfusion

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Editor's key points

- Methylene blue for viral inactivation of fresh-frozen plasma (MB-FFP) is widely used in Europe.
- Description of previously unreported IgE-mediated anaphylaxis to MB-FFP.
- This risk seems to be low in view of the widespread use of this blood product.

Methylene blue-treated fresh-frozen plasma (MB-FFP) is mainly used in Europe. The advantage of the methylene blue system is that units can be treated individually. The combined action of methylene blue and illumination is a photodynamic process preventing viral RNA and DNA replication. We report the first immediate allergic hypersensitivity reaction to methylene blue-treated plasma transfusion. The clinical course and subsequent assessment of the allergic reaction, including skin tests and basophil activation test, confirmed methylene blue-induced IgE-mediated anaphylaxis. All immediate reactions after MB-FFP transfusion should be investigated to document the underlying mechanism.

Keywords: anaphylaxis; basophil degranulation test; fresh-frozen plasma; methylene blue; skin tests

Accepted for publication: 8 November 2010

The use of methylene blue (MB) for viral inactivation of fresh-frozen plasma was originally developed in Germany, and routine production of methylene blue-treated fresh-frozen plasma (MB-FFP) for clinical use started in 1992.¹ Currently, MB-FFP is used more widely in Europe than in the USA. We describe a case of immediate hypersensitivity to MB during MB-FFP transfusion for massive acute gastrointestinal bleeding. Subsequent investigation of the allergic reaction identified the allergen and showed that the underlying mechanism was MB-induced IgE-mediated anaphylaxis.

A 22-yr-old man was admitted to the intensive care unit for severe haematemesis after non-steroidal anti-inflammatory drugs taken for a few days. Laboratory tests showed severe anaemia (Hb 4.8 g dl⁻¹) and coagulation disorders. Red blood cell transfusion was uneventful. In contrast, a few minutes after transfusion of the first MB-FFP pack, he developed peripheral arterial desaturation (SpO₂ 90%), facial angioedema, generalized urticaria, arterial hypotension (a decrease from 132/56 to 80/25 mm Hg), and tachycardia (from 100 to 130 beats min⁻¹). No bronchospasm was noted. MB-FFP transfusion was immediately stopped. Fluid therapy with crystalloids (lactated Ringer's

solution, 1000 ml) and colloids (Voluven®, 500 ml) produced a rapid cardiovascular stabilization and, after chlorphenamine 5 mg, the cutaneous manifestations subsided after 3 h. The subsequent course was uneventful and he was discharged home a few days later.

With the patient's consent, skin testing was performed 6 weeks later using standardized procedures. The skin-prick test (PT) to methylene blue was negative, but the intradermal test (IDT) was positive (10⁻² dilution). All skin tests were negative with patent blue and latex. The MB IDT (10⁻² dilution) was negative in four controls. The serum tryptase level, measured 2 h after the clinical reaction, was eight times higher (8.7 µg litre⁻¹) when compared with basal tryptase (1.1 µg litre⁻¹), although it remained within the normal range (<11.4 µg litre⁻¹). The basophil activation test (BAT) was performed as previously described² with several MB concentrations (5 mg ml⁻¹ to 0.04 µg ml⁻¹). Expression of two activation markers (CD63 and CD203c) was analysed with a FACSCanto II flow cytometer (Becton-Dickinson, Rungis, France). MB at a concentration of 0.2 µg ml⁻¹ induced CD63 expression on 9% of the patient's basophils, compared with 2% of basophils treated with buffer alone. The

manufacturer recommends a positivity cutoff of 5%, and all four controls we tested had values below this threshold (not shown). The CD63 BAT was negative with patent blue. No CD203c up-regulation was observed in response to MB or patent blue.

One advantage of the MB system is that individual units can be treated, whereas FFP is pooled before solvent/detergent treatment. The infection risk associated with plasma transfusion is similar to that associated with other blood components, unless pathogen-reduced plasma is used. MB is a polyaromatic cationic dye of the phenothiazine group which intercalates into viral nucleic acid. The combined action of MB and illumination is a photodynamic process which generates singlet oxygen, leading to guanosine oxidation and destruction of viral nucleic acid.¹ Blood transfusion guidelines recommend an MB concentration below 30 µg per unit in the UK and below 30 µg litre⁻¹ in France.^{3, 4} The UK Department of Health requires that pathogen-reduced plasma should always be used for patients up to 16 yr of age,⁵ whereas patients of all ages who are likely to be exposed to many doses of FFP, such as during plasma exchange, may receive pathogen-reduced FFP.⁶ In France, MB-FFP is commonly used for both adults and children. Haemolysis, transfusion-related acute lung injury, and allergic reactions have all been reported after FFP transfusion.⁶ In contrast, MB-induced anaphylaxis has only been reported twice, after non-systemic administration in both cases.^{7, 8} The first case involved severe IgE-mediated anaphylaxis after intrauterine MB instillation to verify tubal permeability.⁷ Severe arterial hypotension and bronchospasm occurred 2 min after MB instillation. All the symptoms resolved with epinephrine, fluid therapy, and salbutamol. The second case involved a patient with breast cancer undergoing surgery with sentinel node mapping.⁸ Two minutes after subdermal MB injection in the peri-areolar region, she developed severe hypotension, tachycardia, bronchospasm, and hypoxia. All the symptoms resolved with epinephrine, fluid therapy, and corticosteroids. In both cases, the aetiology was supported by MB PT positivity.

This is the first case of anaphylaxis to be reported after systemic MB exposure. The time of onset after MB-FFP transfusion, the clinical manifestations, biological findings, and skin test results confirmed IgE-mediated MB-induced anaphylaxis. We confirm that the comparison of tryptase serum levels during the reaction and in basal conditions some weeks later is more informative than a single post-reaction assay.⁹ PT with methylene blue was negative, but the MB IDT at 10⁻² dilution was positive, confirming that the IDT should be performed when the PT is negative with blue dyes.¹⁰ Flow cytometry of CD63 expression confirmed basophil sensitization by MB-specific IgE, highlighting the importance of this tool in the diagnosis of anaphylaxis.

Allergic IgE-mediated reactions to MB are rare. Patent blue violet (patent blue V) and its derivative isosulfan blue are widely used for sentinel lymph node procedures in breast

cancer patients, in Europe and the USA, respectively. In contrast to MB, allergic reactions to patent blue V and isosulfan blue are frequently reported.^{7, 10} Patent blue V and isosulfan blue belong to the group of triarylmethane dyes. They basically share the same formula and cross-react in skin tests. MB has a structure unrelated to that of these two triarylmethane dyes and does not cross-react with them,^{7, 10} as confirmed in our patient.

Interestingly, MB is a guanylyl cyclase inhibitor and also interferes with nitric oxide-mediated vascular smooth muscle relaxation. Increased nitric oxide synthesis contributes to hypotension and resistance to vasopressors during vasodilatory shock, as in anaphylactic reactions, and MB has been successfully used in catecholamine-resistant anaphylaxis.¹¹

In conclusion, we report the first case of MB-induced anaphylaxis after MB-FFP transfusion. The risk seems to be very low in view of the widespread use of this blood product.¹ However, we recommend extensive investigation of all immediate reactions to MB-FFP transfusion, based on tryptase assay, skin tests, and the BAT, in order to document the mechanism.

Conflict of interest

None declared.

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