

Clinical Guideline

METHYLENE BLUE (METHYLTHIONIUM CHLORIDE) FOR VASOPLEGIA IN CRITICAL CARE (UNLICENSED AND NON-FORMULARY)

SETTING	Adult Intensive Care Units (ICUs) – A600, C604 and Weston ICU UHBW Critical Care areas (General, Cardiac and Weston)
FOR STAFF	ICU nurses, advanced critical care practitioners and medical staff
PATIENTS	Patients with severe vasoplegic shock, with causes including but not limited to, post cardiopulmonary bypass, sepsis and toxicology.

GUIDANCE

Indication	<p>Methylene blue can be used to reverse vasoplegia when other alternatives have failed.</p> <p>It competitively inhibits nitric oxide by binding to the iron haem-moiety of soluble guanylate cyclase enzyme. Guanylate cyclase increases cGMP and thereby calcium extrusion from vascular smooth muscle causing vasodilation. Thus, methylene blue counteracts the effects of nitric oxide and other nitrovasodilators.</p> <p>In patients with vasodilatory shock requiring vasopressor support, methylene blue may reduce the duration of the vasoplegic syndrome and the need for excessive noradrenaline doses.</p>
ONLY TO BE INITIATED ON CONSULTANT ADVICE	
<p>To be considered in vasoplegic shock states, which are worsening and resistant to a combination of ALL the following treatments:</p> <ul style="list-style-type: none">- Adequate intravenous filling- Noradrenaline dose >0.5mcg/kg/min- Vasopressin dose >0.02 units/min- Vasopressor dose steroids (Hydrocortisone 50mg QDS IV)- Appropriate reductions in ino-dilator agents, whilst maintaining an adequate cardiac output. <p>A form of cardiac output monitoring or echocardiogram must confirm a vasoplegic state prior to administration.</p> <p>Methylene blue is <u>unlicensed</u> for the indication of vasoplegic shock. It is also non-formulary, so formulary paperwork is required for each patient use but do not delay treatment – see ICU Pharmacist for</p>	

assistance.

Background information	Patients with severe vasoplegic shock are difficult to treat, with excessive doses of catecholamines causing serious side effects. Drugs which act on non-catecholamine receptors and pathways can improve vasoplegia and limit the doses and potentially serious side effects of excessive exogenous catecholamines. Vasoplegia causes include, but are not limited to, post cardiopulmonary bypass, sepsis and toxicology.
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Prescribing and administration	Incompatible with sodium chloride - NEEDS TO BE FLUSHED WITH GLUCOSE 5%. Dosage should be calculated on LEAN body weight. Central venous administration is recommended. Peripheral venous administration should only be performed in an emergency – <i>do not exceed a 1mg/ml infusion concentration.</i> All below details assume a central venous administration:
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Initial Bolus:

- 1-2mg/kg, made up to 50mls total volume with 5% glucose
- Administer over 15-60mins

Ongoing therapy: If there is a positive response to the initial bolus, ongoing treatment can be via either repeated boluses or an infusion:

Repeated boluses	Continuous infusion
1-2mg/kg, made up to 50mls total volume with 5% glucose. Administer over 15-60mins. Repeat every 2-3 hours as required.	500mg Methylene Blue in 5% glucose to a total volume of 250mls (2mg/ml). Administer at 0.25 - 2mg/kg/hr (0.125 – 1mls/kg/hr). Start the infusion 2 hours after the initial bolus.

Available as both a 5mg/ml and 10mg/ml preparation – caution with which preparation is used for dilution.

Use with caution in renal impairment (consider reducing dose of the bolus to <1mg/kg and using the lower end of the infusion range).

No experience in patients with severe hepatic impairment.

Compatibility

Compatible: (where medicines meet close to the vascular access device)²:

Glucose 5%

Considerations

The MHRA have issued the following advice on use of methylene blue:

- Intravenous methylthioninium chloride should be avoided in patients who have been treated recently with serotonergic antidepressants, including SSRIs, clomipramine, and venlafaxine
- If use of intravenous methylthioninium chloride cannot be avoided, the lowest possible dose should be used and the patient observed closely for CNS effects for up to four hours after administration
- If features of CNS toxicity develop after use of methylthioninium, the patient should be monitored closely and given supportive care.

Adverse effects

- Dizziness, headache, tremors, and mental confusion
- Falsely low oxygen saturations on SpO₂ monitoring
- Cardiac arrhythmias.

Monitoring/ considerations

- Minimise the dose delivered.
- Monitor for CNS side effects during administration and for 4 hours after delivery
- Instigate supportive care if CNS adverse effects occur.
- Monitor SpO₂ continuously during and for 4 hours post administration. Supplemental oxygen as required.
- Check saturations and PaO₂ with an arterial blood gas if the oxygen saturations appear falsely low.
- Consider reducing the dose of methylene blue or other vasoactives and treat with anti-arrhythmic drugs if required.

- Hypertension
 - Monitor fluid status and consider reducing the dose of methylene blue or other vasopressors.
- Hypotension
 - Monitor fluid status and consider increasing the dose of other vasopressors.
- Nausea
 - Consider anti-emetics.
- Blue discolouration of urine, stools and saliva.
 - Reassurance to those caring for the patient.
- Methaemoglobinemia
 - Monitor Met-Hb levels on gases every 4 hours if an infusion or repeated boluses are being used. If the Met-Hb is >5%, reduce or stop the infusion and do not give further boluses.

Table A

REFERENCES	<ol style="list-style-type: none"> 1. Shanmugam G. Vasoplegic syndrome – the role of methylene blue. European Journal of Cardio-thoracic surgery 2005; 705-710 2. Fischer GW, Levin MA. Vasoplegia during cardiac surgery: Current concepts and management. Sem Thorac Cardiovasc Surg 2010; 22(2):140-144. 3. MHRA Drug Safety Update April 2009. Methylthioninium chloride (methylene blue): Update on CNS toxicity with serotonergic drugs 4. Vutskits L, Briner A, Klauser P et al. Adverse effects of Methylene Blue on the Central Nervous System. Anesthesiology 2008; 108:684-92 5. Ibarra-Estrada, M., Kattan, E., Aguilera-González, P. et al. Early adjunctive methylene blue in patients with septic shock: a randomized controlled trial. <i>Crit Care</i> 27, 110 (2023). 6. Royal Brompton and Harefield Hospitals Clinical Guidelines - Methylene Blue (Methylthioninium Chloride). 7. Medusa: online via http://medusa.wales.nhs.uk/IVGuideDisplay.asp. (via Trust intranet). Methylthioninium chloride Accessed 10/05/23. 8. TOXBASE: Online via https://www.toxbase.org . Methylene Blue (antidote). Accessed 10/05/23.
RELATED DOCUMENTS AND PAGES	<ul style="list-style-type: none"> - Noradrenaline in Critical Care – awaited - Vasopressin – ICU Sharepoint and DMS - Management of cardiogenic and mixed shock in critical care – ICU Sharepoint.
AUTHORISING BODY	Critical Care Executive - awaited
SAFETY	See document for safety issues.
QUERIES AND CONTACT	In an emergency contact the Critical Care Pharmacy team or the Senior ICU medical team (Phone 27139). For non-emergency advice, contact the Critical Care Pharmacy team or Matt Govier (matthew.govier@uhbw.nhs.uk – ICU consultant).
AUDIT REQUIREMENTS	Datix review.

**Document Change
Control**

Date of Version	Version Number	Lead for Revisions	Type of Revision	Description of Revision
May 2023	1.00	MG (ICU Cons)	Initial	Initial document