Methylene Blue
Newborn use only

2022

Alert	It should be prescribed in mg/kg **(NOT mL/kg)** as potential dosing error can occur between mg and mL. Methylene blue is also known as methylthioninium chloride.
Indication	Methaemoglobinaemia
Action	In the red blood cell, methylene blue is reduced to leukomethylene blue. Leukomethylene blue then interacts with methaemoglobin (MetHb) to reduce the ferric iron back to ferrous iron.[1,2]
Drug type	Antidote for methaemoglobinaemia
Trade name	Methylene Blue Injection (Phebra). Proveblue (Clinect).
Presentation	Methylene Blue Injection contains methylene blue trihydrate 50 mg/5 mL (10 mg/mL) (= 1%). Proveblue contains methylene blue trihydrate 50mg/10mL (5 mg/mL) (= 0.5%).
Dose	**1 mg/kg/dose** Dose can be repeated after 1 hour if MetHb remains over 30% or remain symptomatic.[1, 5]
Dose adjustment	Therapeutic hypothermia – No information. ECMO – No Information. Renal impairment – Use with caution in severe renal impairment. Hepatic impairment – No information.
Maximum dose	2 mg/kg/**dose** (not per day)
Total cumulative dose	
Route	IV
Preparation	Administer undiluted. If required can be diluted with dextrose 5% only. .
Administration	IV infusion over 5 minutes. Line can be flushed with sodium chloride 0.9% to reduce venous irritation.
Monitoring	MetHb concentration at 1 hour after the dose (Neofax states to monitor MetHb during treatment and until resolution of methaemoglobinaemia). Pulse oximetry for at least 24 hours. FBC: 24 hours after the dose (earlier if concerns of haemolytic anaemia). Extravasation: Methylene blue has a pH of 3 – 4.5 and extravasation may cause tissue necrosis.
Contraindications	Hypersensitivity to any component of methylene blue.
Precautions	Severe renal insufficiency[4] G6PD deficiency[4]
Drug interactions	
Adverse reactions	Dose-related toxicity is described.[4] At 2-4 mg/kg/dose: Haemolytic anaemia, skin desquamation. At >4 mg/kg/dose: Blue-green discolouration of urine and faeces. At 7 mg/kg/dose: Nausea, vomiting, abdominal pain, fever, haemolysis. At 20 mg/kg/dose: Hypotension. At 80 mg/kg/dose: Bluish discolouration of skin (similar to cyanosis). This can be treated topically with diluted hypochlorite solution. Methylene blue is an oxidant and itself can increase MetHb concentrations.[2] Risk of anaphylaxis.
Compatibility	Fluids: Glucose 5%.[5] Y-site: Not tested.
Incompatibility	Fluids: Sodium chloride 0.9%, sodium chloride 0.45%, all strengths of sodium chloride + glucose combination fluids. Y-site: Not tested.
Stability	Use immediately. Discard unused portion.
Storage	Store below 25°C. Protect from light.
Excipients	Methylene Blue Injection: Water for injections, sodium hydroxide and/or hydrochloric acid.[3] Proveblue: Water for injections.

Special comments	Methylene Blue Injection should not be diluted with sodium chloride 0.9% as precipitation may occur (due to presence of chloride ions which have been shown to reduce the solubility of methylene blue).[3]
Evidence	**Background** Methaemoglobin (MetHb) level in the human body is usually maintained below 1.5% of total haemoglobin.[2] Symptomatic methaemoglobinaemia is usually observed when MetHb concentrations exceed 15%.[1] **Efficacy** Treatment of choice for methaemoglobinaemia is 1 mg/kg of methylene blue infused intravenously over 5 minutes. Additional doses can be given if symptoms persist or methaemoglobin levels remain high. The suggested high MetHb concentrations varied from 30% to 60%.[1, 2, 4, 7] **Safety** Methylene blue has dose-related toxicity.[4] Even 2 mg/kg/dose can rarely cause haemolytic anaemia. Methylene blue doses over 4 mg/kg can exhibit an oxidizing effect and result in haemolysis and methaemoglobin production. Methaemoglobinaemia in these individuals is best treated with blood transfusions.[4] **Pharmacokinetics** After IV administration, time to reach peak effect is within 30 minutes. It is eliminated in bile, faeces and urine as leukomethylene blue.[4]
Practice points	
References	1. Berant R, Ratnapalan S. A pale baby with blue blood. Pediatric Emergency Care. 2015;31(10):713-4. 2. Johnson SF. Methemoglobinemia: Infants at risk. Current Problems in Pediatric and Adolescent Health Care. 2019;49(3):57-67. 3. Methylene blue injection. Phebra Pty Ltd. MIMS online accessed online on 7 April 2022. 4. Clifton J, 2nd, Leikin JB. Methylene blue. American Journal of Therapeutics. 2003;10(4):289-91. 5. Methylene blue. Micromedex online. Accessed on 8 April 2022. 6. Methylene blue. Australian injectable drugs handbook, 8th edition. Accessed online on 8 April 2022. 7. Ward J, Motwani J, Baker N, Nash M, Ewer AK, Toldi G. Congenital Methemoglobinemia Identified by Pulse Oximetry Screening. Pediatrics. 2019;143(3):03.

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