

Methylene Blue Solution for Injection

Methylthioninium chloride trihydrate 10mg/mL

Name of Drug

The active ingredient of Methylene Blue Solution for Injection is methylene blue trihydrate (3,7-Bis(dimethylamino)phenazathionium chloride trihydrate).

Presentation

Methylene Blue Solution for Injection is a clear, blue-coloured solution containing in each 5.0 mL glass ampoule, methylene blue trihydrate 50.0 milligrams and water for injections. The pH of the solution ranges between 3.0 and 4.5.

Uses

Actions

In patients with methaemoglobinaemia, therapeutic doses of methylene blue can lower the levels of methaemoglobin in red blood cells. It activates a normally dormant reductase enzyme system that reduces the methylene blue to leucomethylene blue, which in turn is able to reduce methaemoglobin to haemoglobin. However, in large doses, methylene blue can itself produce methaemoglobinaemia and the methaemoglobin concentration should therefore be closely monitored during treatment. Methylene blue is not effective for the treatment of methaemoglobinaemia in patients with glucose-6-phosphate dehydrogenase deficiency as these patients have a diminished capacity to reduce methylene blue to leucomethylene blue. It is also potentially harmful as patients with glucose-6-phosphate dehydrogenase deficiency are particularly susceptible to the haemolytic anaemias induced by methylene blue.

Methylene blue also possesses weak antiseptic and bacteriological staining properties and is reported to inhibit amine oxidase in tissues. The drug appears to bind irreversibly to viral nucleic acid and cause disruption of the virus molecule upon exposure to light.

The use of methylene blue as a diagnostic aid is based on its ability to stain tissue. Any skin discolouration can be removed with hypochlorite solution.

Pharmacokinetics

In tissues, methylene blue is rapidly reduced to leucomethylene blue, which is stabilised as an undetermined salt, complex, or combination form in the urine but not in the blood.

About 75% of an oral dose of methylene blue is excreted in the urine, primarily as leucomethylene blue, although a small proportion is excreted as the unchanged drug, while some is excreted via the bile.

Indications

Methylene Blue Solution for Injection is indicated:

- For the treatment of drug-induced methaemoglobinaemia
- For the treatment of idiopathic methaemoglobinaemia (in which a structural abnormality of haemoglobin is not present)
- As a bacteriological stain
- As a dye in diagnostic procedures such as fistula detection
- For the delineation of certain body tissues during surgery.

Dosage and administration

Methylene blue may be administered orally or by intravenous injection. In the treatment of acute methaemoglobinaemia, the intravenous route of administration is usually preferred because it provides a more rapid onset of effect.

Adults and children

In the treatment of methaemoglobinaemia, methylene blue is administered intravenously as a 1% solution in doses of 1 to 2 milligrams per kg bodyweight injected over a period of several minutes. A repeat dose may be given after one hour if required. A maximum dose of 7 milligrams per kilogram body weight is recommended. The use of methylene blue is not recommended in infants under 4 months of age.

A dose of 5 mg/kg diluted in 500 mL of saline (sodium chloride 0.9%) or glucose 5% infused over 1 hour has been used successfully to stain and identify the parathyroid glands.

A suitable dilution for oral dosing would be 5 to 10 mL of the 1% solution diluted to 100 to 200 mL with water for injection. The high volume is suggested to reduce the degree of gastrointestinal disturbances and dysuria.

The dosage of methylene blue should be calculated on the basis of lean bodyweight.

Contraindications

Methylene Blue Solution for Injection is contraindicated in the following circumstances:

- Known hypersensitivity to the drug
- Patients with severe renal impairment
- Patients with glucose-6-phosphate dehydrogenase deficiency
- Methaemoglobinaemia due to chlorate poisoning
- Methaemoglobinaemia during treatment of cyanide poisoning.

Intrathecal and subcutaneous injection of methylene blue are also contraindicated, as they can result in neural damage (intrathecal administration) and necrotic abscess (subcutaneous administration).

Warnings and precautions

Long-term use

Long-term administration of methylene blue may result in marked anaemia due to accelerated destruction of erythrocytes; haemoglobin concentrations should be checked frequently.

If methylene blue is injected subcutaneously or if extravasation occurs, necrotic abscesses may result (see Contraindications).

CNS Toxicity

The use of methylene blue for localization in parathyroid surgery is not an approved indication. Adverse CNS effects including confusion, disorientation, agitation and expressive aphasia, altered muscle tone in limbs, hypoxia, ocular symptoms, and depressed level of consciousness have been reported following intravenous infusion of methylene blue for parathyroid surgery.

Serotonin Syndrome

Spontaneous reports of serotonin syndrome associated with the co-administration of methylene blue and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have been reported. Co-administration of methylene blue and serotonergic agents is therefore not recommended except where administration of methylene blue and concomitant serotonergic agents is essential. In those cases the lowest possible dose should be used and patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia, clonus and incoordination. If signs or symptoms occur physicians should consider discontinuing either one or both agents; if the concomitant serotonergic agent is withdrawn, discontinuation symptoms can occur.

Use in children

Safety and efficacy of methylene blue in infants have not been established. It has been reported that the metabolism of methylene blue to leucomethylene blue is likely to be less efficient in neonates, due to reduced efficiency of NADPH-diaphorase in this age group. The use of Methylene Blue Solution for Injection in infants up to 4 months of age is not recommended.

Use in renally impaired patients

Methylene blue is excreted mainly via the urine, primarily as leucomethylene blue. Methylene Blue Solution for Injection is contraindicated in patients with severe renal impairment. Caution should be exercised when administering methylene blue to patients with mild to moderate renal impairment.

Effect on laboratory tests

Phenolsulfophthalein excretion test: methylene blue may cause false positive test results.

Pulse oximetry: methylene blue may result in an underestimation of the oxygen saturation reading.

Patient monitoring

Full blood count, including reticulocyte count should be undertaken to ensure haemolysis has not occurred.

Long term administration of methylene blue may result in anaemia. Haemoglobin levels should be monitored during long-term therapy.

Methaemoglobin levels should be monitored throughout therapy.

Carcinogenicity, mutagenicity, impairment of fertility

There is no information on the carcinogenic potential of methylene blue.

Methylene blue was positive to gene mutation assays in bacteria and mouse lymphoma cells, but was negative in the in vivo mouse micronucleus test.

In vitro, methylene blue has been shown to reduce motility of human sperm. It has also been shown to inhibit the growth of cultured two-cell mouse embryos and the production of progesterone in cultured human luteal cells. In vivo effects on fertility and reproduction are not known.

Pregnancy and Lactation

Use in pregnancy - Category D

Methylene blue should not be administered to pregnant women.

Use in lactation

There is no information on whether or not the drug crosses into breast milk. Safety in the newborn has not been established, and hence it is recommended that breastfeeding is discontinued prior to administration of Methylene Blue Solution for Injection.

Effects on ability to drive and use machines

Methylene Blue Solution for Injection is likely to produce minor or moderate adverse effects, which may impair the patient's ability to concentrate and react and therefore constitute a risk in the ability to drive and use machines.

Adverse effects

The following adverse events have been reported after intravenous administration of methylene blue:

Gastrointestinal: nausea, vomiting, diarrhoea, abdominal pain, blue colour of faeces and saliva.

Haematologic: haemolysis (in glucose-6-phosphate dehydrogenase deficiency, or high doses), methaemoglobinaemia (after high doses).

Cardiovascular: hypertension, hypotension, arrhythmia, chest pain.

Body as a whole: profuse sweating.

Dermal: rash (blue macules, severe burning pain).

Nervous System: headache, dizziness, mental confusion. Serotonin syndrome.

Injection site: thrombophlebitis (resulting from high doses, if not adequately diluted - not more than 350 milligrams of methylene blue should be diluted in each 500 mL of infusion fluid), necrosis (if extravasation occurs).

Renal: blue color of urine.

Oral administration may cause gastrointestinal disturbances and dysuria.

Use of methylene blue for endoscopic tattoo has been associated with vascular necrosis, mucosal ulceration, mural necrosis, extramural fat necrosis and inflammatory changes in the colon.

Injection of methylene blue into joint space has resulted in effusion in the treated joint.

Interactions

Methylene blue is an inhibitor of monoamine oxidase (MAOI). Therefore administration to patients taking serotonergic medicines is not recommended unless absolutely necessary (see warnings and precautions).

Overdosage

No specific information is available. However, large doses of methylene blue can produce methaemoglobinaemia. Side effects seen with high doses include chest pain, dyspnoea, restlessness, apprehension, tremors and a sense of oppression. Large doses are irritant to the urinary tract. In addition, it can produce a mild haemolysis with moderate hyperbilirubinaemia, reticulosis and slight anaemia. Rarely, however, severe haemolytic anaemia with Heinz body formation has resulted. Methylene blue in large doses could cause a blue discolouration of the skin after methaemoglobin levels have returned to normal.

Treatment of overdosage

There is no specific antidote for methylene blue overdose. Treatment is symptomatic and supportive. In severe and refractory cases of methaemoglobinaemia, blood transfusions and even exchange transfusions and (possibly) hyperbaric oxygen may be the only alternative available.

Pharmaceutical precautions

Incompatibilities

Methylene blue is reported to be incompatible with caustic alkalis, iodides and dichromates, and oxidising and reducing substances.

Special Precautions for Storage

Store below 25°C. Protect from light.

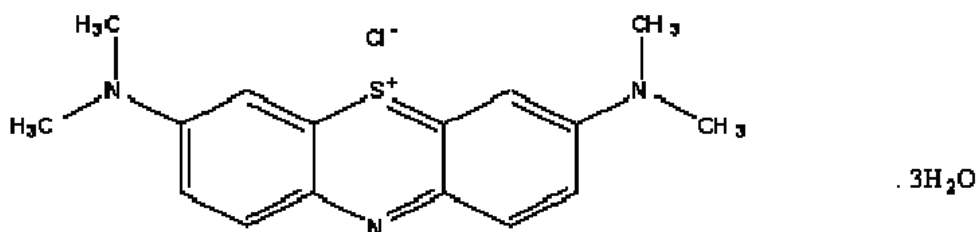
Medicine classification

Prescription Medicine

Further information

Methylene blue is a dark green, odourless or almost odourless, crystal or crystalline powder. It is soluble in water, alcohol and chloroform. The molecular formula of methylene blue is $C_{16}H_{18}ClN_3S \cdot 3H_2O$. It has a molecular weight of 373.9 and its CAS registry number is 7220-79-3.

The structural formula of methylene blue trihydrate is shown below:



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