METHYLENE BLUE (Systemic)

Introduction

INN: Methylthioninium chloride 2

VA CLASSIFICATION (Primary/Secondary)¾AD900/DX900
Commonly used brand name(s):Urolene Blue.
Other commonly used names are aniline violet 18 , methylthionine chloride 1, 18 , and tetrametylthionine chloride 5, 6 .

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

Category

Antimethemoglobinemic; diagnostic aid (tissue dye).

Indications

Accepted

Methemoglobinemia, acquired (treatment) and

Methemoglobinemia, idiopathic (treatment)¾Methylene blue is indicated in the treatment of acquired and idiopathic methemoglobinemia. 7, 9, 17, 18, 20, 24, 27, 29

Tissue dye in diagnostic procedures¾Methylene blue is used as a bacteriological stain, 7, 18, 27 as a dye in diagnostic procedures, such as fistula detection, 21, 27 and for the selective staining of certain body tissues during surgery. 7, 27 Methylene blue is also used intraamniotically to diagnose premature rupture of fetal membranes 22, 24 and to identify separate amniotic sacs in twin pregnancies. 24, 27

Unaccepted

Methylene blue has been used to produce methemoglobinemia in the treatment of cyanide poisoning; 18 however, sodium nitrite is considered to be a safer, more effective alternative. Methylene blue has been used as a urinary tract antibacterial agent; 1, 18, 22 however, this medication has been replaced by more effective agents. 18

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Molecular weight¾373.90 2, 18

pH¾3 to 4.5 19

Mechanism of action/Effect:

Methemoglobinemia¾Methylene blue, in low concentrations, acts as a cofactor to accelerate the conversion of methemoglobin to hemoglobin in erythrocytes. 1, 6, 7, 8, 9, 12, 13, 18, 20, 23, 29 Methylene blue combines with nicotinamide adenine dinucleotide phosphate reduced (NADPH), in the presence of NADPH-methemoglobin reductase, to produce leukomethylene blue; leukomethylene blue then reduces methemoglobin to hemoglobin. 5, 6, 11, 12, 20, 27

Tissue dye¾Methylene blue's usefulness as a diagnostic aid is based on its ability to stain tissue. 1, 7

Other actions/effects:

In high concentrations, methylene blue oxidizes the ferrous iron of hemoglobin to the ferric state, facilitating the conversion of hemoglobin to methemoglobin. 1, 6, 7, 9, 18, 23, 24, 27, 29

Methylene blue has mild antiseptic activity 1, 18, 22 that may inhibit bacterial proliferation.

Absorption:

Poorly absorbed from the gastrointestinal tract after oral administration. 5, 6, 20

Biotransformation:

Rapidly reduced to leukomethylene blue. 1, 5, 6, 18

Elimination:

Excreted in the urine 1, 6, 17, 20, 27 and bile, 6 primarily as leukomethylene blue. Some unchanged drug is also excreted in the urine. 1, 27

Precautions to Consider

Pregnancy/Reproduction

Pregnancy¾Studies have not been done in humans. 9

Studies have not been done in animals. 1

FDA Pregnancy Category C.

Breast-feeding

It is not known whether methylene blue is distributed into breast milk. 1 However, problems in humans have not been documented.

Pediatrics

Extreme caution should be exercised when administering methylene blue to infants. During the first 4 months of life, 5, 8 infants have lower concentrations of the enzymes necessary for reducing methemoglobin to hemoglobin, making these infants more susceptible to methemoglobinemia 3, 5, 6, 8, 10, 15, 27 produced by high doses of methylene blue.
Intraamniotic injection of methylene blue has resulted in hemolytic anemia, hyperbilirubinemia, methemoglobinemia, and deep blue staining of the newborn. 22, 23, 24, 25

Geriatrics

Appropriate studies on the relationship of age to the effects of methylene blue have not been performed in the geriatric population. However, no geriatrics-specific problems have been documented to date.

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With diagnostic test results

>> Phenolsulfonphthalein (PSP) excretion test 26

(methylene blue may cause a false positive test result)

Urinary free formaldehyde and

Urine pH

(methylene blue may interfere with analysis)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problems exist

>> Glucose-6-phosphate dehydrogenase (G6PD) deficiency 1, 3, 4, 6, 8, 11, 12, 18, 20, 27

(use of methylene blue may aggravate methemoglobinemia and precipitate hemolytic anemia)

>> Methemoglobinemia, to treat cyanide toxicity 5, 20

(methylene blue increases release of cyanide from methemoglobin, increasing the concentration of cyanide in the blood)

Risk-benefit should be considered when the following medical problems exist

Renal function impairment 1, 17, 27

(elimination may be reduced; dosage reduction may be required)

Sensitivity to methylene blue 1, 20

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
Complete blood counts and

>> Reticulocyte counts 20

(recommended following methylene blue therapy to assure that hemolysis has not occurred)

>> Methemoglobin concentrations 3, 4, 11, 20

(recommended 1 to 2 hours following administration of methylene blue to assess the effectiveness of therapy)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Greenish blue to blue discoloration of urine 1, 4, 6, 18, 26, 27 and feces 1, 18, 27
Incidence less frequent

Diarrhea 1, 18; nausea and vomiting 1, 18, 27; painful urination or increased urinary frequency 1, 4, 6, 18, 20, 27¾with oral administration

Overdose

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Clinical effects of overdose

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Abdominal pain 5, 7, 8, 18, 29; anxiety 5, 6, 10, 20; chest pain 3, 5, 6, 7, 8, 18, 20; confusion 5, 7, 8, 18, 29; electrocardiographic changes (diminished or inverted T wave amplitude; diminished R wave

amplitude) 5, 10; hemolytic anemia (abdominal, back, or leg pain; chills) 3, 11, 12, 14, 17, 27; methemoglobinemia (bluish fingernails, lips, or skin; difficulty in breathing; dizziness; headache; unusual tiredness or weakness) 1, 3, 5, 6, 7, 8, 10, 11, 12, 14, 18, 20, 24, 27, 29; nausea and vomiting 1, 5, 7, 8, 29; severe sweating 8, 18, 29; tremors 3, 5, 6, 20

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Methylene Blue (Systemic).
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Sensitivity to methylene blue
Use in children¾Cautious use in infants up to 4 months of age because they have lower concentrations of enzymes that reduce methemoglobin to hemoglobin; intraamniotic injection may cause hemolytic anemia, hyperbilirubinemia, methemoglobinemia, or deep blue staining of newborn
Other medical problems, especially glucose-6-phosphate dehydrogenase (G6PD) deficiency and methemoglobinemia to treat cyanide toxicity
Proper use of this medication

Taking tablets after meals with a full glass (240 mL) of water

>> Proper dosing
Missed dose
>> Proper storage
Precautions while using this medication

Possible interference with laboratory values

Side/adverse effects

Greenish blue to blue discoloration of urine and feces may be alarming to patient although medically insignificant

General Dosing Information

Treatment of acquired methemoglobinemia should be initiated with general supportive care and removal of the toxic agent, which, depending on the severity of the poisoning, may include administering 100% oxygen, 5, 12, 20 and removing the toxic agent from the body. This can be done by removing contaminated clothing and rinsing the skin with water, inducing emesis, instituting gastric lavage, administering activated charcoal and cathartic, 4, 5, 6, 10, 20 or instituting hemodialysis. 4, 6, 11 In most cases of methemoglobinemia, these treatment measures stabilize the patient. 4, 5, 12

Specific antidotal therapy with methylene blue should be reserved for cases of methemoglobinemia in which the methemoglobin concentration is greater than 30% or in which there are clinical signs of hypoxia. 6, 8, 10, 11, 20

If adequate methylene blue therapy fails and toxic concentrations of methemoglobin persist, the possibility of glucose-6-phosphate dehydrogenase (G6PD) deficiency, 5, 6, 8, 10, 11, 12, 13, 20, 27 nicotinamide adenine dinucleotide phosphate reduced (NADPH) methemoglobin reductase deficiency, 5, 6, 8, 10, 13, 20, 27 hemoglobin M, 8, 10, 13 or sulfhemoglobinemia 5, 6, 8, 10, 12, 20 should be considered. In these cases, exchange transfusion 3, 5, 6, 10, 13, 20 may be required. Hyperbaric oxygen 8, 10 has also been recommended, 6, 8, 10, 11 but its efficacy in this setting has been questioned and there is little experience with its use. 11

Chronic, idiopathic methemoglobinemia usually requires treatment only for cosmetic purposes. 3, 4 Administration of ascorbic acid, orally or intravenously, 100 to 500 mg two or three times a day is a non-toxic alternative to methylene blue. Ascorbic acid usually maintains the methemoglobin concentration below the level that causes cyanosis, preventing a cyanotic appearance. 3, 6, 20 However, ascorbic acid reduces methemoglobin to hemoglobin too slowly to be of benefit in the treatment of acquired methemoglobinemia. 4, 6, 8, 11

For oral dosage forms only

Methylene blue tablets should be taken after meals with a full glass (240 mL) of water. 1, 18

For parenteral dosage forms only

Methylene blue should be administered by intravenous injection. Subcutaneous or intrathecal injection may result in tissue necrosis 5, 9, 27 or neural damage, 9, 27 respectively.

Oral Dosage Forms

METHYLENE BLUE TABLETS

Usual adult and adolescent dose

Methemoglobinemia, idiopathic¾
Oral, 100 to 300 mg per day. 3, 4, 27

Usual adult prescribing limits

7 mg per kg of body weight. 30

Strength(s) usually available

U.S.¾65 mg (Rx)[Urolene Blue] [Generic]

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light. 1

Auxiliary labeling:

· Take after meals with a full glass (240 mL) of water.
· May discolor urine and/or stools.

Parenteral Dosage Forms

METHYLENE BLUE INJECTION USP

Usual adult and adolescent dose

Methemoglobinemia¾
Intravenous, 1 to 2 mg per kg of body weight 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 16, 17, 18, 20, 27, 28, 29 or 25 to 50 mg per square meter of body surface area, 20 administered over five minutes. 5, 6, 8, 10, 20 The dose may be repeated after one hour if needed. 3, 4, 5, 6, 8, 11, 12, 20, 27

Note: For treatment of methemoglobinemia following overdose of agents in which there is prolonged or continuous methemoglobin formation (e.g., dapsone), methylene blue may be administered by continuous intravenous infusion at a rate of 0.1 to 0.15 mg per kg of body weight per hour, following an initial dose of 1 to 2 mg per kg of body weight. 13, 14

Usual adult prescribing limits

7 mg per kg of body weight. 3, 5, 8, 11, 20

Usual pediatric dose

See Usual adult and adolescent dose.

Strength(s) usually available

U.S.¾10 mg per mL (Rx) [Generic]

Canada¾10 mg per mL (Rx) [Generic]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), 21, 29 unless otherwise specified by manufacturer. Protect from light. 21

Preparation of dosage form:

For continuous intravenous infusion, methylene blue should be admixed with a compatible solution, such as 0.9% sodium chloride injection, to a final concentration of 0.05%. 14

Auxiliary labeling:

· May discolor urine and/or stools.