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Review Article

Methylene blue and its role in ICU patients. A Review

***Pradeep M Venkategowda, Mithilesh K Raut,**
Surya P Yarramalle and Yogesh R
Critical Care Madicine, Yashoda Hospital,
Somajiguda, Hyderabad, Telangana, India.
*Corresponding Author: drpradeepmarur@gmail.com

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ABSTRACT:

Methylene blue (MB) has multiple applications in ICU patients. Used as antidote in case of methemoglobinemia, as rescue therapy in case of refractory septic shock and anaphylactic shock, for treatment and / prophylaxis in case of Ifosfamide related neurotoxicity. Methylene blue acts by inhibiting both inducible nitric oxide synthase (iNOS) and soluble guanylate cyclase (sGC) of vascular smooth muscle cells along with decreasing the levels of sGC, scavenging nitric oxide (NO) and inhibition of NO synthesis which overall results in hemodynamic stability (basis of treatment in refractory septic shock and anaphylactic shock). It is a reducing agent at physiological doses hence used in patients with methemoglobinemia. Methylene blue also acts as alternate electron acceptor and restores the mitochondrial respiratory chain which is the basic defect in Ifosfamide related neurotoxicity.
It can cause multiple side effects which are transient at physiological doses. Most common side effect is discoloration of body fluids. Methylene blue is widely recommended as an antidote in methemoglobinemia, but the exact role in case of refractory septic shock, anaphylactic shock and Ifosfamide induced neurotoxicity should be confirmed by large observational studies. This review article summarizes the mechanism of action, different uses and complications associated with Methylene blue use in ICU.

KEY WORDS: Methylene blue, Septic shock, Nitric oxide, Methemoglobinemia, Anaphylaxis, Ifosfamide, Bluish discoloration, Greenish urine.

INTRODUCTION:

Methylene blue is a heterocyclic aromatic compound with molecular weight of 371.923 and a chemical formula C16H18Cl N3S·3H20. At room temperature it is a solid, dark green powder, on mixing with water or alcohol produces blue solution. Methylene blue was first prepared in 1876 by German chemist-Heinrich Caro. In 1891 it was first used by Paul Guttmann and Paul Ehrlich to treat malaria [1].

It has been used in various clinical conditions such as septic shock, methemoglobinemia, anaphylactic shock, urinary tract leaks or fistula detection, Ifosfamide related neurotoxicity, submucosally during endoscopic polypectomy to identify submucosal plane, as a spray in detection of dysplasia or precancerous lesion in gastrointestinal tract (chromoendoscopy), with bone cement to discriminate between native bone and cement and to accelerate the hardening of bone cement, priapism, cyanide [2] and carbon monoxide poisoning, sentinel lymph node dissection, vasoplegia [3,4] following cardiac surgery, psoriasis [5], AIDS related Kaposi's sarcoma [6], West Nile virus infection [7] and as placebo [8]. It has been administered at various routes such as Intravenous, Oral, Local site (Submucosal), Intra-amniotic to confirm rupture of membranes [9] and intrathecal to look for reperfusion lung injury following superior mesenteric artery clamping/unclamping [10].

Methylene blue is administered enterally or intravenously as 1% solution (10 mg/ml). Oral absorption is about 53% to 97% [11] and likely undergoes first pass metabolism. Peak effect is seen at 1-2 hours of injection with a half life of 5– 6.5 hours. It is in excreted in urine, feces and bile [12]. MB should be avoided in patients with known previous allergy to it, patients having G6PD deficiency, low levels of NADPH and severe renal failure.

Sepsis related immune dysregulation causes systemic inflammatory response syndrome, characterized by release of cytokines and endotoxins [13,14]. These endotoxins (causes increased production of iNOS) [15-17] and cytokines (causes release of iNOS in target cells) causes production of NO from vascular smooth muscle cells. This NO causes vasodilatation through activation sGC and increasing the concentration of cGMP (Guanosine mono phosphate). Methylene blue has shown to restore hemodynamics through NO mediated mechanism [18-21] and its administration has shown to reverse hemodynamic deterioration and prevent the development of severe septic shock. Methylene blue has been used in refractory hypotension in both immuno-competent and immuno-suppressed patients, anaphylactic shock following contrast during coronary angiogram, methemoglobinemia and Ifosfamide induced neurotoxicity.

USES IN ICU:

1. **Septic shock**: During sepsis, the cytokines, endotoxins and thrombin which are produced in our body causes production of nitric oxide (NO). NO is produced by two types of nitric oxide synthases (NOS) in our body, such as constitutive endothelial nitric oxide synthase (eNOS) and an inducible nitric oxide synthase (iNOS) [11]. The constitutive eNOS which is present within vascular endothelium is stimulated by thrombin and shear stress, produces lesser amount of NO and hence maintains basal vascular tone [22]. The iNOS is synthesized within vascular smooth muscle cells (cytokines and /or endotoxins produced during sepsis causes synthesis of iNOS) [23] and in turn produces NO. This NO stimulates soluble guanylate cyclase (sGC) within the smooth muscles to produce guanosine 3'-5' monophosphate (cGMP) which leads to smooth muscle cell relaxation (vasodilatation). The cytokines can also cause synthesis of iNOS within cardiac muscles leading to cGMP mediated decreased myocyte contraction [24,25]. In lungs it can produce impaired gas exchange, vascular leak and organ failure [26-28].

Methylene blue acts by inhibiting both inducible nitric oxide synthase (iNOS) and soluble guanylate cyclase (sGC) of vascular smooth muscle cells [29,30]. It also acts by decreasing the levels of sGC, scavenging NO, inhibition of NO synthesis [31] and competitive action with NO [32], which overall results in hemodynamic stability.

In many case reports, MB has been used as a last resort for treatment of intractable septic shock in

the form of intravenous bolus (1-2mg/kg) or short term infusion for <6 hours [33-39]. Tristan et al [40] have used MB infusion for about 120 hours in Wegener's granulomatosis patient on chronic prednisone and azathioprine treatment who had refractory septic shock (100mg of MB intravenous bolus initially followed by 0.5mg/kg/hr and further tapering dose up to 120 hours).

Sarvanan et al have used MB (100mg infused over 2 hours) even in immunosuppressed patient after liver transplantation in severe sepsis with good effect [41]. Alhameed et al [42] used methylene blue bolus (1 mg/kg) followed after 2 h by infusion at 0.5 mg/kg/h for 4 hours as an adjuvant treatment to patients with septic shock and concluded that continuously infused MB for 4 hours counteracts myocardial depression, reduces adrenergic support and maintains oxygen transport as compared with conventional treatment alone.

Even though there are no guidelines for use of MB in refractory septic shock, many case reports have shown the usefulness in the form of hemodynamic stability and mortality benefits when MB was used as last resort. Large observational studies are required to recommend its use in septic shock patients along with dosage and duration of infusion.

2. **Methemoglobinemia** (MHb):

MHb occurs due to oxidation of ferrous iron (Fe^{++}) to ferric iron (Fe^{+++}) within hemoglobin [43]. MHb can cause impaired oxygen transport leading to tissue hypoxia, cyanosis, metabolic acidosis and death (if severe methemoglobinemia present). Causes of methemoglobinemia (MHb) are multifactorial, such as idiopathic, genetic (cytochrome-b5 reductase deficiency or cytochrome-b5 deficiency), acidosis, dietary (well water containing nitrates) and exposure to oxidizing agents (such as aniline, benzocaine, dapsone, nitrites and nitrates) [44].

Small amount of MHb is formed continuously in our body endogenously, since the RBCs are bathed in blood. Endogenous reducing system in our body keeps MHb levels to about 1% every time [45]. The enzymatic systems which are involved in maintaining lower levels of MHb are cytochrome-b5 - MHb reductase system (99% of daily MHb reduction) and ascorbic acid, glutathione, flavin, tetrahydropterin and cysteamine [46] as a minor system. Cytochrome b5 and cytochrome-b5 reductase transfer electrons from NADH (formed from glycolysis) to MHb to form reduced hemoglobin.

The NADPH–MHb reductase also known as generalized reductase, under normal conditions plays a minor role in reducing MHb to hemoglobin. It can reduce methylene blue due to its affinity [47-49], which in turn reduces MHb to hemoglobin. MHb levels more than 10% causes cyanotic discoloration of skin, >20% causes anxiety and headache, >30% fatigability, >50% coma and death at >70%.

MHb can be detected at bedside with 3 simple tests. Test-1: Placing 1-2 drops of patient blood on white filter paper turns the dark red color of deoxyhemoglobin to bright red (exposure to atmospheric oxygen) where as the chocolate brown color of MHb remains the same. Test-2: The potassium cyanide test, which distinguishes between sulfhemoglobin and MHb.

MHb reacts with cyanide to form cyanomethemoglobin which is bright red in color as opposed to the chocolate brown color of MHb whereas Sulfhemoglobin is similar in appearance to MHb and does not change in color after exposure to potassium cyanide [50]. Test-3: when MHb level reaches about 30-35%, the pulse oximeter will show saturation of about 82-86% (Fixed range) but the Pao_2 levels will be high.

This treatment is usually started when MHb is about 20% in symptomatic and 30% in asymptomatic patient [51].

Patients having anemia, heart disease, lung disease and carbon monoxide poisoning, treatment may be initiated at lower levels also. The treatment of choice is MB. Methylene blue is a reducing agent at pharmacological doses, whereas at higher doses it acts as an oxidizing agent. The dose is about 1-2 mg/kg infused (IV) over 3-5 minutes. If MHb does not resolve within 30 minutes then MB can be repeated at 1 mg/kg [52].

3. **Anaphylactic shock**:

Nitric oxide plays an important role during pathophysiology of anaphylaxis. In vitro it antagonizes the effects of vasoconstrictors released by anaphylaxis. Except for vasodilatation, NO production reduces pathophysiological changes associated with anaphylaxis [53]. Rodrigues et al have reported the usefulness of methylene blue in both anaphylaxis and anaphylactic shock [54]. Methylene blue was used during anaphylaxis and anaphylactic shock with a dose of 1.5-2 mg/kg intravenous bolus with good outcome. Evora et al [55] used intravenous bolus of methylene blue (1.5-2 mg/kg) who developed anaphylactic shock following injection of radiocontrast media during coronary angiography with good immediate response. They observed chest pain and nodal rhythm in one patient. The nodal rhythm returned to normal spontaneously within a minute. Zheng et al have shown that in case of anaphylactic shock both epinephrine and methylene blue had synergistic effect [56].

Even though many case reports suggest single bolus of Methylene blue during anaphylactic shock has a role, but large observational study is essential to recommend its definitive role.

4. **Ifosfamide neurotoxicity**:

Ifosfamide is prodrug, metabolized to its alkylating agents (by cytochrome p450) such as 4-hydroxy-ifosfamide and isofosforamide. It is used in the treatment of soft tissue sarcoma, cervical carcinoma and germ cell tumors. Ifosfamide induced encephalopathy is seen in 10-15% of patients treated with it.

The exact pathophysiological mechanism is unknown. The non-alkylating metabolites (chloracetaldehyde) are thought to be responsible for the neurotoxicity toxicity of Ifosfamide. The metabolite chloroethylamine, on conjugation with cysteine forms thialysine which later metabolized to thialysine ketimine.

This inhibits the flavoproteins in the mitochondrial respiratory chain leading to accumulation of NADH. The other metabolite chloracetaldehyde (neurotoxic substance) needs NAD for the oxidation.

Hence decreased levels of NAD can cause accumulation of chloracetaldehyde and precipitates neurotoxicity.

Methylene blue acts as an alternate electron acceptor (replacing the inhibited flavoproteins) and restores the mitochondrial respiratory chain [57], MB also causes dehydrogenation of the aldehydes by oxidating NADH [58]. Methylene blue has also been found to inhibit the plasma and extrahepatic monoamine oxidases [59] which can also form chloracetaldehyde.

There are many case reports which used MB for the treatment of Ifosfamide induced encephalopathy [60-62]. Pelgrims et al [59] in their literature review regarding the role of MB in the treatment of Ifosfamide induced encephalopathy (between 1993 and 1997) involving 52 patients who received Ifosfamide had following findings.

Twelve patients developed encephalopathy out of which 8 patients received MB (300mg/day). Four patients recovered within 24 hours, 2 patients recovered after 48 hours and remaining 2 patients recovered after 72 hours.

Later authors concluded that MB can be used in a dose of 300 mg /day (IV) for treatment and 200 mg /day (IV/orally) for secondary prophylaxis of Ifosfamide-induced encephalopathy.

COMPLICTIONS: The complications due to MB have been shown in table-1.

Table-1: Showing complications related to Methylene blue administration.

SYSTEMS	CLINICAL FEATURES
Hematological	Heinz body hemolytic anemia [64] and Hyperbilirubinemia (in G6PD deficiency patients). Methemoglobinemia (higher doses). Anaphylactic reaction [65].
Respiratory	Increased pulmonary vascular resistance (mainly with bolus doses) [66,67]. Falsely low oxygen saturation [68].
Central nervous system	Dizziness, confusion, fever, headache, diaphoresis and serotonin syndrome [69].
Cardiovascular system	Hypertension, arrhythmias (transient ventricular ectopics and nodal rhythms) and coronary vasoconstriction (angina) [70,71].
Skin	Bluish discoloration of palms, soles and face. Necrosis at injection site [72]. Epithelial desquamation following phototherapy in infants [73].
Genito-urinary	Greenish urine [74]. Transient elevation in alanine and aspartate amino transferases.
Gastro-intestinal	Nausea, vomiting, abdominal pain and decreased splanchnic perfusion (at bolus of 7mg/kg).

Most common side effect is the discoloration of body fluids [63]. Methylene blue can cause Heinz body hemolytic anemia and hyperbilirubinemia in patients having G6PD deficiency and lower levels of NADPH. With bolus doses it can cause increased pulmonary vascular resistance. Methylene blue causes bluish discoloration of palms, soles, face and body fluids. Transient nodal rhythms and ventricular ectopics are seen. Higher doses can cause coronary and splanchnic vasoconstriction. Fever, headache, confusion, dizziness and serotonin syndrome are seen in patients on mono amino oxidase inhibitors. Locally it can cause skin necrosis. Rare complications include anaphylaxis and epithelial desquamation during phototherapy

CONCLUSION:

Methylene blue has wide variety of application in the ICU. It is used as an antidote in methemoglobinemia, but the exact role in case of refractory septic shock, anaphylactic shock and Ifosfamide induced neurotoxicity should be confirmed by large observational studies.

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REFERENCES:

1. Guttmann P, Ehrlich P. On the effect of methylene blue on malaria. Berliner Klinische Wochenschrift 1891;28:953-956.
2. Matilda MB. Methylene blue as an antidote for cyanide and carbon monoxide poisoning. The Scientific Monthly1936;43:585–586.
3. Levin RL, Degrange MA, Bruno GF, Del Mazo CD, Taborda DJ, Griotti JJ et al. Methylene blue reduces mortality and morbidity in vasoplegic patients after cardiac surgery. Ann Thorac Surg 2004;77: 496–9.
4. Stawicki SP, Sims C, Sarani B, Grossman MD, Gracias VH. Methylene blue and vasoplegia: who, when, and how. Mini Rev Med Chem 2008;8:472–90.
5. Salah M, Samy N, Fadel M. Methylene blue mediated photodynamic therapy for resistant plaque psoriasis. J Drugs Dermatol 2009;8:42–9.
6. Tardivo J.P, Del Giglio A, Paschoal L.H, Baptista MS. New photodynamic therapy protocol to treat AIDS-related Kaposi's sarcoma. Photomed Laser Surg 2006;24:528–31.
7. Papin JF, Floyd RA, Dittmer DP. Methylene blue photoinactivation abolishes West Nile virus infectivity in vivo. Antiviral Res 2005; 68:84–7.

8. Novella S. The ethics of deception in medicine. Science Based Medicine 2008:01-24.
9. McEnerney JK, McEnerney LN. Unfavorable neonatal outcome after intraamniotic injection of methylene blue. Obstet Gynecol 1983;61:35-37.
10. Weinbroum AA. Methylene blue attenuates lung injury after mesenteric artery clamping/unclamping. Eur J Clin Invest 2004;34:436-42.
11. Shanmugam G. Vasoplegic syndrome – the role of methylene blue. Eur J Cardiothorac Surg 2005;28:705-710.
12. Allegaert K, Miserez M, Lerut T, Naulaers G, Vanhole C, Devlieger H. Methemoglobinemia and hemolysis after enteral administration of methylene blue in a preterm infant: relevance for pediatric surgeons. J Pediatr Surg 2004;39:11.
13. Lyn-Kew K, Standiford TJ. Immunosuppression in sepsis. Current Pharmaceutical Design 2008;14:1870–1881.
14. Boomer JS, Chang KC, Takasu O, Osborne DF, Walton AH, Bricker TL, Jarman SD et al. Immunosuppression in patients who die of sepsis and multiple organ failure. The Journal of the American Medical Association 2011;306:2594–2605.
15. Laffi G, Foschi M, Masini E, Simoni A, Mugnai L, La Villa G et al. Increased production of nitric oxide by neutrophils and monocytes from cirrhotic patients with ascites and hyperdynamic circulation. Hepatology 1995;22:1666–1673.
16. Galley HF, Coomansingh D, Webster NR, Brunt PW. Nitric oxide synthase activity is increased in relation to the severity of liver dysfunction. Clinical Science 1998;95:355–359.
17. Nathan C, Xie QW. Nitric oxide synthases: roles, tolls, and controls. Cell 1994;78:915–918.
18. Levin RL, Degrange MA, Bruno GF, Del Mazo CD, Taborda DJ, Griotti JJ et al. Methylene blue reduces mortality and morbidity in vasoplegic patients after cardiac surgery. Annals of Thoracic Surgery 2004;77:496–499.
19. Fischer GW, Bengtsson Y, Scarola S, Cohen E. Methylene blue for vasopressor-resistant vasoplegia syndrome during liver transplantation. Journal of Cardiothoracic and Vascular Anesthesia 2010;24:463–466.
20. Brown G, Frankl D, Phang T. Continuous infusion of methylene blue for septic shock. Postgraduate Medical Journal 1996;72:612–614.
21. Kwok ESH, Howes DW. Use of methylene blue in sepsis: a systematic review. Journal of Intensive Care Medicine 2006;21:359–363.
22. Singh S, Evans TW. Nitric oxide, the biological mediator of the decade: fact or Fiction. Eur Respir J 1997;10:699-707.
23. Vincent JL, Zhang H, Szabo C, Preiser JC. Effects of nitric oxide in septic shock. Am J Respir Crit Care Med 2000;161:1781-1785.
24. Schultz R, Nava E, Moncada S. Induction and potential biological relevance of a Ca-dependent nitric oxide synthase in the myocardium. Br J Pharmacol 1992;105:575-580.
25. Grayling M, Deakin CD. Methylene blue during cardiopulmonary bypass to treat refractory hypotension in septic endocarditis. J Thorac Cardiovasc Surg 2003;125:426-427.
26. Grocott-Mason RM, Shah AM. Cardiac dysfunction in sepsis: new theories and clinical implications. Intensive Care Med 1998;24:286-295.
27. Kumar A, Brar R, Wang P, Dee L, Skroupa G, Khadour F et al. Role of nitric oxide and cGMP in human septic serum-induced depression of cardiac myocyte contractility. Am J Physiol 1999;276:265-276.
28. Brady AJ, Poole-Wilson PA, Harding SE, Warren JB. Nitric oxide production within cardiac myocytes reduces their contractility in endotoxemia. Am J Physiol 1992;263:1963-1966.
29. Mayer B, Brunner F, Schmidt K. Inhibition of nitric oxide synthesis by methylene blue. Biochem Pharmacol 1993;4:367-74.
30. Paya D, Gray GA, Stoclet JC. Effects of methylene blue on blood pressure and reactivity to norepinephrine in endotoxemic rats. J Cardiovasc Pharmacol 1993;2:926-30.
31. Marczin N, Ryan US, Catravas JD. Methylene blue inhibits nitro vasodilator

and endothelium-derived relaxin factor-induced cyclic GMP accumulation in cultured pulmonary arterial smooth muscle cells via generation of superoxide anion. J Pharmacol Exp Ther 1992;263:170-179.
32. Yiu P, Robin J, Pattison CW. Reversal of refractory hypotension with single dose methylene blue after coronary artery bypass surgery. J Thorac Cardiovasc Surg 1999;118:194-195.
33. Schneider F, Lutun P, Hasselmann M, Stoclet JC, Tempe JD. Methylene blue increases systemic vascular resistance in human septic shock. Preliminary observations. Intensive Care Med 1992;18:309-11.
34. Kwok ES, Howes D. Use of methylene blue in sepsis: a systematic review. J Intensive Care Med 2006;2:359-63.
35. Kirov MY, Evgenov OV, Evgenov NV, et al. Infusion of methylene blue in human septic shock: a pilot, randomized, controlled study. Crit Care Med 2001;29:1860-7.
36. Koch HJ. Effects of methylene blue in septic shock. Crit Care Med 1996;24:1093-4.
37. Marczin N, Tekeres M, Salzman AL, Szabo C. Methylene blue infusion in septic shock. Crit Care Med 1995;23:1936-8.
38. Schneider F. Methylene blue infusion in septic shock. Crit Care Med 1995;23:1935-6.
39. Weingartner R, Oliveira E, Oliveira ES, et al. Blockade of the action of nitric oxide in human septic shock increases systemic vascular resistance and has detrimental effects on pulmonary function after a short infusion of methylene blue. Braz J Med Biol Res 1999;32:1505-13.
40. Tristan CD, Samuel M, Colin KY, Robert G. Prolonged methylene blue infusion in septic shock: a case report. Can J Anesth 2011;58:401-405.
41. Saravanan R, Shachi P, Eric B, Zakiyah K, Tadahiro U, Piotr K et al. Use of methylene blue for treatment of severe sepsis in an immunosuppressed patient after liver transplantation. Case Reports in Transplantation 2013;2013:1-4.
42. Abd-Alhameed AE, Hamed MS, Omran AS. Methylene blue: Role in early management of septic shock patients. Ain-Shams Journal of Anesthesiology 2014; 07:327–335.
43. Stryer L, Freeman WH. Oxygen transporting proteins in Biochemistry. Ed 3 1988:143-171.
44. Zinkham WH, Oski FA, Henna. A potential cause of oxidative hemolysis and neonatal hyperbilirubinemia. Pediatrics 1996;97:707-709.
45. Jaffe ER, Hultquist DE, Scriver CR, Beaudet AL, Sly WS et al. Cytochrome b5 reductase deficiency and enzymopenic hereditary methemoglobinemia. The Metabolic and Molecular Basis of Inherited Disease 1995:2267-2280.
46. Jaffe ER. Enzymopenic hereditary methemoglobinemia: A clinical/biochemical classification. Blood Cells 1986;12:81-90.
47. Metz EN, Balcerzak SP, Sagon LR. Mechanism of methylene blue stimulation of the hexose monophosphate shunt in the erythrocyte. J Clin Invest 1976;58:797-802.
48. Benatti U, Guida L, Grasso M, Tonetti M, De Flora A, Winterbourn CC. Hexose monophosphate shunt-stimulated reduction of methemoglobin by divicine. Arch Biochem Biophys 1985;242:549-556.
49. Ashmun RA, Hultquist DE, Schultz JS. Kinetic analysis in single, intact cells by microspectrophotometry: Evidence for two populations of erythrocytes in an individual heterozygous for glucose-6-phosphate dehydrogenase deficiency. Am J Hematol 1986;23:311-316.
50. Evelyn KA, Malloy HT. Microdetermination of oxyhemoglobin, methemoglobin and sulfhemoglobin in a single sample of blood. J Biol Chem 1938;126:655-662.
51. Price D. Methoglobinemia, in Goldfrank LR, Flomenbaum N, Lewin N et al. Goldfrank's Toxicologic Emergencies, ed 6. Old Tappan, NJ: Appleton Lange, 1998:1507-1523.
52. Finch CA. Treatment of intracellular methemoglobinemia. Bull N Engl Med Ctr 1947;9:241-245.
53. Mitsuhata H, Shimizu R, Yokoyama MM. Role of nitric oxide in anaphylactic shock. J Clin Immunol 1995;15:277-83.

54. Rodrigues JM, Filho AP, Rodrigues AJ, Vicente WV, Evora PR. Methylene blue for clinical anaphylaxis treatment: a case report. Sao Paulo Med J 2007;125:60-2.
55. Evora PR, Oliveira Neta AM, Duarte NM, Vicente WV. Methylene blue as treatment for contrast medium-induced anaphylaxix. J Postgrad Med 2002;48:327.
56. Zheng F, Barthel G, Collange O, Montémont C, Thornton SN, Longrois D et al. Methylene blue and epinephrine: a synergetic association for anaphylactic shock treatment. Crit Care Med 2013;41:195-204.
57. Harpey JP, Charpentier C, Coudé M. Methylene blue for riboflavinunresponsive glutarica ciduria type II. Lancet 1986; I:391.
58. Hrushesky WJ, Olshefski R, Wood P, Meshnick S, Eaton JW. Modifying intracellular redox balance: an approach to improving therapeutic index. Lancet I 1985:565–567.
59. Aeschlimann C, Cerny T, Küpfer A. Inhibition of (mono) amine oxidase activity and prevention of ifosfamide encephalopathy by methylene blue. Drug Metab Disp 1996;24:1336–1339.
60. Alonso JL, Nieto Y, López JA, Martín M, Díaz-Rubio E. Ifosfamide encephalopathy and methylene blue: a case report. Ann Oncol 1996;7: 643–645.
61. Cerny T, Castiglione M, Brunner K, Küpfer A, Martinelli G, Lind M. Ifosfamide by continuous infusion to prevent encephalopathy. Lancet 1990;335:175.
62. DiMaggio JR, Brown R, Baile WF, Schapira D. Hallucinations and ifosfamide-induced neurotoxicity. Cancer 1994;73:1509–1514.
63. Gachot B, Bedos JP, Veber B, Wolff M, Regnier B. Short-term effects of methylene blue on hemodynamics and gas exchange in humans with septic shock. Intensive Care Med 1995; 21:1027-31.
64. Sills MR, Zinkham WH. Methylene blue induced Heinz body hemolytic anemia. Arch Pediatr Adolesc Med 1994;148:306-319.
65. Dewachter P, Mouton-Faivre C, Trechot P, Lleu JC, Mertes PM. Severe anaphylactic shock with methylene blue instillation. Anesth Analg 2005;101:149-150.
66. Evora PR, Roselino CH, Schiavetto PM. Methylene blue in anaphylactic shock. Ann Emerg Med 1997;30:240.
67. Evora PR. Should methylene blue be the drug of choice to treat vasoplegias caused by cardiopulmonary bypass and anaphylactic shock (letter). J Thorac Cardiovasc Surg 2000;119:632-634.
68. Kessler MR, Eide T, Humayun B, Poppers PJ. Spurious pulse oximeter desatiration with methylene blue injection. Anesthesiology 1986;65:435-436.
69. Sweet G, Standiford SB. Methylene-blue-associated encephalopathy. J Am Coll Surg 2007;204:454-458.
70. Almeida JA, Riordan SM, Liu J, Galhenage S, Kim R, Bihari D, Wegner EA, Cranney GB, Thomas PS. Deleterious effects of nitric oxide inhibition in chronic hepatopulmonary syndrome. Eur J Gastroenterol Hepatol 2007;19:341-46.
71. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864-874.
72. Stradling B, Aranha G, Gabram S et al. Adverse skin lesions after methylene blue injections for sentinel lymph node localization. Am J Surg 2002;184:350- 352.
73. George MD. Methylene-blue induced hyperbilirubinemia and phototoxicity in a neonate. Clin Pediatr 2000;39.
74. Yap KP, Chng HC. Urinary discoloration after rectal instillation of methylene blue dye. Singapore Med J 2003;44:268.