CLINICAL PHARMACOLOGY

Methylene Blue: Revisited

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Methylene blue, an inhibitor of nitric oxide synthase and guanylate cyclase has many uses in medicine. It has been found to improve the hypotension associated with various clinical states.[1] It also improves hypoxia and hyper dynamic circulation in cirrhosis of liver and severe hepatopulmonary syndrome.[2] It also results in transient and reproducible improvement in blood pressure and cardiac function in septic shock.[3]

METHYLENE BLUE IN CATECHOLAMINE REFRACTORY VASOPLEGIA

Vasoplegic syndrome is generally defined as an arterial pressure <50 mm Hg, cardiac index >2.5 L /min/m^2, right atrial pressure <5 mm Hg, left atrial pressure <10 mm Hg and low systemic vascular resistance <800 dyne/sec/cm^5.[4]

Risk factors for vasoplegia

Recent studies have established various risk factors for postoperative vasoplegia. These include preoperative use of heparin, ACE inhibitors, congestive heart failure, poor left ventricular function, duration of cardiopulmonary bypass (CPB), re-operation, age of the patient and opiod anesthesia.[5,6]

Mechanism of action of methylene blue in vasoplegia

It has been suggested that refractory vasoplegia may reflect a dysregulation of nitric oxide synthesis and vascular smooth cell guanylate cyclase activation. Based on recent pathophysiologic findings it appears that the soluble intracellular enzyme guanylate cyclase is activated to produce cyclic guanosine monophosphate (C-GMP) presumably under the influence of several mediators including nitric oxide.[7,8]

Methylene Blue acts by inhibiting guanylate cyclase, thus decreasing C-GMP and vascular smooth muscle relaxation.[9]

Preoperative use in cardiac surgery

Methylene blue (1%) has been used IV over 30 min in ICU 1hour before surgery and found decreased incidence and severity of Vasoplegic syndrome in high risk patients.[4]

Intraoperative

It has also been successfully added to CPB prime (2 mg/kg) and continued as infusion (.25- 2mg/kg/hr) during CPB to treat refractory hypotension in septic endocarditis.[10]

Postoperative

It can also be used to treat severe vasoplegia in post operative transplant patient[11,12]. Hence Studies have concluded decreased mortality in vasoplegic patients after cardiac surgery with methylene blue as compared to placebo.[8]

Dosage

Methylene blue is used as a single dose of 1.5 -2 mg /kg IV over 20 min to 1hr for rescue treatment. [4, 7, 8, 11, 13]

METHYLENE BLUE IN SEPTIC SHOCK

A release of nitric oxide has been incriminated in the cardiovascular alterations of septic shock. Since guanylate cyclase is the target enzyme in the endothelium dependent relaxation mediated by nitric oxide, Methylene blue- a potent inhibitor of guanylate cyclase has been found very effective in improving the arterial pressure and cardiac function in septic shock.[3]

Studies have found improvement in mean arterial pressure (MAP) and systemic vascular resistance (SVR) while decreasing vasopressor requirements in septic shock.[14]

METHYLENE BLUE AND HEPATOPULMONARY SYNDROME

The hypoxemia in hepatopulmonary syndrome results from widespread pulmonary vasodilatation due to increased C-GMP. Methylene blue is found to ↑PaO2 and ↓alveolar-arterial difference for partial pressure of oxygen in all pts

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with hepatopulmonary syndrome. This was due to ↓C-GMP levels by Methylene Blue-a potent inhibitor of guanylate cyclase.[2]

METHYLENE BLUE AS ANTIMALARIAL

Methylene Blue has already been used some 100 yr ago against malaria, but it disappeared when chloroquine (CQ) and other drugs entered the market. However recent studies has shown the efficacy of Methylene Blue as an effective and cheap antimalarial agent especially in countries with increasing resistance of P. falciparum to existing 1st line antimalarial agents-CQ and pyrimethamine-sulfadoxine.

Methylene Blue, a specific inhibitor of P.falciparum glutathione reductase has the potential to reverse CQ resistance and it prevents the polymerization of haem into haemozoin similar to 4-amino-quinoline antimalarials.

A dose of 36-72mg/kg over 3 days is the most effective schedule.[15]

Apart from the intrinsic antimalarial activity and CQ sensitizing action it was also considered to prevent methemoglobinemia- a serious complication of malarial anemia.[16]

METHYLENE BLUE IN METHEMOGLOBINEMIA

Methemoglobinemia is a life threatening condition that can be congenital or acquired. It is characterized by the inability of hemoglobin to carry oxygen because the ferrous part of the heme molecule has been oxidized to a ferric state.

Methylene Blue acts by reacting within RBC to form leukomethylene blue, which is a reducing agent of oxidized hemoglobin converting the ferric ion (fe^{+++}) back to its oxygen carrying ferrous state(fe^{++}).[17]

Dose commonly used is 1-2mg/kg of 1% Methylene Blue solution.[17,18]

METHYLENE BLUE AND CANCER

Recent research suggests that Methylene Blue and other redox cyclers induce selective cancer cell apoptosis by NAD (P) H: quinine oxidoreductase (NQO1)-dependent bioreductive generation of cellular oxidative stress. Hence Methylene Blue is being investigated for the photodynamic treatment of cancer.[19]

IFOSFAMIDE NEUROTOXICITY

Another, less well known use of Methylene Blue is its utility for treating ifosfamide neurotoxicity. A toxic metabolite of ifosfamide, chloroacetaldehyde, disrupts the mitochondrial respiratory chain, leading to accumulation of nicotinamide adenine dinucleotide hydrogen (NADH).

Methylene blue acts as an alternative electron acceptor, and reverses the NADH inhibition of hepatic gluconeogenesis while also inhibiting the transformation of chloroethylamine into Chloroacetaldehyde, and also inhibits multiple amine oxidase activities, preventing the formation of Chloroacetaldehyde.[20]

Hence it has prophylactic and therapeutic role in ifosfamide - induced encephalopathy.[21]

METHYLENE BLUE AS DYE AND STAIN

Methylene blue infusion was found as a safe and effective method of localizing abnormal parathyroid glands.[22]

Methylene blue has also been used for intraoperative endoscopic marking of intestinal lumen for location of lesions.[23]

Methylene blue was also found as an effective and cheap alternative to isosulfan blue dye for sentinel lymph node localization in pt with breast cancer.[24]

Methylene blue also has been used in diagnostic microbiology as a stain. It is an inexpensive and rapid method for detection of H.pylori.[25]

NEUTRALIZATION OF HEPARIN

Methylene blue effectively neutralizes heparin especially in pts with protamine allergy. However work still needs to be done to determine the safety of the drug at the higher doses necessary to neutralize heparin levels achieved in bypass patients.[26]

METHYLENE BLUE AND PRIAPISM

Methylene blue has been used to treat high flow priapism by intra-cavernous injection which is known to antagonize endothelial derived relaxation factor.[27]

METHYLENE BLUE AND ALZHEIMER'S DISEASE

The relationship between Methylene blue and Alzheimer's disease has recently attracted increasing scientific attention. It has been shown to attenuate the formations of amyloid plaques and neurofibrillary tangles and partial repair of impairments in mitochondrial function and cellular metabolism.[28]

METHYLENE BLUE COMBINED WITH LIGHT

Photodynamic therapy using the light activated anti-microbial agent, Methylene blue kills methicillin resistant staphylococcus aureus (MRSA) in superficial and deep excisional wounds.[29] Methylene blue in combination with light also inactivates viral nucleic acid of hepatitis-C and human immunodeficiency virus (HIV-1) and treats cases of resistant plaque psoriasis.[30,31]

ADVERSE EFFECTS

Methylene blue is a safe drug when used in therapeutic

doses (<2mg/kg).But it can cause toxicity in high doses. The features of toxicity being cardiac arrhythmias, coronary vasoconstriction, decreased cardiac output, renal blood flow and mesenteric blood flow; increased pulmonary vascular pressure & pulmonary vascular resistance and gas exchange deterioration. It also turns urine greenish blue and bluish discoloration of skin and mucosa which is self limiting.[4, 7]

Due to its tissue reactive properties, a case of skin and fat necrosis followed by a dry gangrene of the skin in a female patient with breast cancer who underwent sentinel lymph node biopsy localization using peri-tumoral injection of Methylene blue dye has been reported.[32]

It can also cause hemolytic anemia characterized by Heinz body formation especially in pts with severe renal insufficiency and glucose-6-phosphate dehydrogenase (G6PD) deficiency.[18]

Neonates are particularly prone to adverse effects of Methylene blue. It causes hyperbilirubinemia, meth-Hemoglobin formation, hemolytic anemia, respiratory distress, pulmonary edema, photo toxicity and bluish discoloration of tracheal secretions and urine.[33, 34, 35, 36, 37, 38, 39, 40, 41]

Methylene Blue also interferes with the pulse oximeter's light emission resulting in falsely depressed oxygen saturation reading.[18]

Methylene blue due to its monoamine oxidase(MAO) inhibiting property may precipitate potentially fatal serotonin toxicity at doses >5mg/kg [42] and rarely can cause severe anaphylactic shock.[43]

CONTRAINDICATIONS

Methylene blue is contraindicated in patients who have developed hypersensitivity reactions to it and in severe renal insufficiency. It is relatively contraindicated in G6PD deficient patients as it can cause severe hemolysis and also in patients with Heinz body anemia.[18,43]

DRUG INTERACTIONS

Methylene blue is a MAO inhibitor and therefore can interact with selective serotonin reuptake inhibitor (SSRI) and MAO inhibitors to cause serious serotonin toxicity.[42,43]

It also interacts with dapsone and forms hydroxylamine which oxidizes hemoglobin causing hemolysis.[18]

CONCLUSIONS

Methylene Blue was till now known mainly as a dye but is now entering into the field of cardiac surgery and critical care as a very important therapeutic agent with diverse applications. The evidence for its use in methemoglobinemia is well established but that for its use in vasoplegia, septic shock, hepatopulmonary syndrome, malaria,ifosfamide neurotoxicity etc is limited but promising and commands more research.

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