

ACTUALIZĂRI

# Methylene blue, an old drug with new indications?

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## Abstract

Just when we thought we finally understood methylene blue (MB) after it has been used clinically for more than a century, the old properties are revived and therefore possible new indications appears. Nitric oxide (NO) stimulates soluble guanylate cyclase, which converts guanosine triphosphate into cyclic guanosine monophosphate. Increases in cGMP concentration, in turn, through a cascade of protein kinases, induce smooth muscle relaxation and vasodilation. Methylene blue (MB) has direct inhibitory effects on nitric oxide synthases (NOS), both constitutive and inducible and blocks accumulation of cyclic guanosine monophosphate (cGMP) by inhibiting the enzyme guanylate cyclase. Also, MB blocks the iron-containing enzymes such as xanthine oxidase and has antioxidants effects. New indications are therefore described in relation with MB as in the vasoplegic syndrome following cardiopulmonary bypass in humans and in the settings of cardiac arrest in animals.

**Keywords:** methylene blue, oxidative injury, neuroprotection, hemodynamics, cardiopulmonary resuscitation

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## Introduction

Methylene Blue (methylthionine chloride) is a heterocyclic aromatic chemical compound with molecular formula ( $C_{16}H_{18}ClN_3S, 3H_2O$ ) (Fig. 1) with the chemical name [3, 7-bis (Dimethylamino)-phenazathionium chloride Tetramethylthionine chloride] [1, 2]. Methylene blue (MB) is a cationic thiazine dye that is deep blue in the oxidized state while it is colorless in its reduced form (leucomethylene blue) (Table 1). MB and leucomethylene blue exist as a redox couple in equilibrium and together form a reversible oxidation-

reduction system or electron donor-acceptor couple [1].

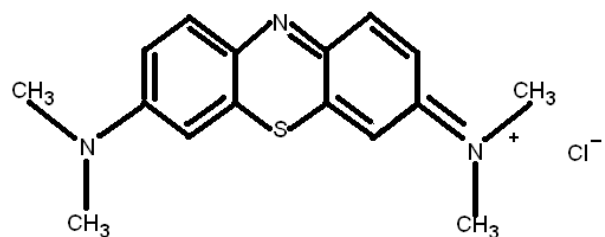


Fig. 1. Chemical structure of methylene blue

## The history of methylene blue

Methylene blue was first prepared by Caro in 1876 as an aniline-derived dye for textiles [2]. However, it is a drug full of surprises that has made history as a histochemical stain, a biochemical reagent and a lead compound in the development of therapeutic agents for diseases ranging from microbial disease to dementia

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[3]. The staining activity of methylene blue, developed by Paul Ehrlich in 1891, provided the foundation of modern chemotherapy [3]. In the late 19<sup>th</sup> and early 20<sup>th</sup> centuries it was used in humans to treat malaria [4], but then ceased to be used as an anti-malarial due to its two inevitable side effects: green urine and blue sclera. Interest in its use has recently been revived, especially because it is very cheap [5]. In the 1920s it proved to be a dramatic antidote for cyanide poisoning, since its reduction potential is similar to that of oxygen and it can be reduced by components of the electron transport chain [3]. Its versatility has allowed MB to

be tested against many other poisons; it miraculously reversed toxic methemoglobinemia, it reversed symptoms of cyclophosphamide – induced encephalopathy and, exotically, those of Jamaican ackee fruit poisoning [6].

MB reverses hypotension in septic shock, is helpful in cases of profound “vasoplegia” following cardiopulmonary bypass, and it may have value in the treatment of protamine reactions. It can help in some cases of anaphylactic shock, and it has helped to treat hypotension related to lithium toxicity, ACE inhibition, and hemodialysis [6].

### Physical and chemical properties and pharmacokinetics of methylene blue (Table 1)

**Table 1.** Physical and chemical properties and pharmacokinetics of MB

Physical and chemical properties	Values	Pharmacokinetics	Properties
Melting temperature	180°	Ionization at gastric pH	Completely at normal gastric pH [7]
Boiling temperature	No data	Oral absorption	53-97% [8]
Solubility in water	35.5g.l <sup>-1</sup>	Peak plasma concentration	After 30-60 min [7, 9]
pH value	3 (10g/l H <sub>2</sub> O)	Volume of distribution	20 ml.kg <sup>-1</sup> [8]
Molecular weight	319 g.mol <sup>-1</sup>	Plasma half-life	5-6 hours [7]
Color	Dark blue-green in oxidized form, colorless in reduced form (leukomethylene blue)	Metabolism	Reduced in peripheral tissues to leukomethylene blue (65-85%) [8]
Chemical formula	C <sub>16</sub> H <sub>18</sub> N <sub>3</sub> ClS	Elimination	Bile, feces and urine as leukomethylene blue [9]

### Administration and dose of methylene blue (Table 2)

**Table 2.** Administration and dose of methylthioninium chloride in humans

Dose	Administration	Duration	Indication
1-2 mg.kg <sup>-1</sup>	Bolus i.v.	10-20 min, 1 hour	Vasodilatation with hypotension [10, 11]
	After bolus i.v. continuous infusion	48-72 h	Vasoplegic syndrome [12]
0.25-1 mg.kg <sup>-1</sup> .h <sup>-1</sup>	Continuous infusion	6 h, 2 h after bolus	Sepsis [13, 14]
1.5-2 mg.kg <sup>-1</sup>	Bolus i.v.		Anaphylactic shock [15]
300 mg.day	Oral doses of up to 300 mg.day <sup>-1</sup>	Daily	Hereditary methemoglobinemia
150 mg.day	Oral doses or i.v.	50 mg three times daily	Encephalopathy after ifosfamide [16]
2 mg.kg <sup>-1</sup>	Bolus i.v.	Before CPB	Surgery for septic endocarditis [17]
0.5 mg.kg <sup>-1</sup> .h <sup>-1</sup>	Continuous i.v. until 30 min after CPB	3 h	Cardiopulmonary bypass [10, 18], patients on angiotensin-converting agents after start of CPB [15]

## Toxicity of methylene blue (Table 3)

**Table 3.** Dose-related toxicity of MB

Animal studies	Toxic doses	Manifestation
Rat [19]	5-50 mg.kg <sup>-1</sup> 1250 mg.kg <sup>-1</sup> (LD50)	Neuronal apoptosis, reduced MAC isoflurane
Mouse	3500 mg.kg <sup>-1</sup>	
Sheep [20]	40 mg.kg <sup>-1</sup>	
Dog [21]	10-20 mg.kg <sup>-1</sup>	Hypotension, decreased SVR, renal blood flow, pulmonary hypertension
Human studies	Dose (mg/kg)	Toxic manifestations [18, 22]
	2-4	Hemolytic anemia, skin desquamation in infants
	7	Nausea, vomiting, abdominal pain, chest pain, fever, hemolysis
	7.5	Hyperpyrexia, confusion
	20	Hypotension
	80	Bluish discoloration of skin (similar to cyanosis)

### Effects of MB on nitric oxide synthase and guanylyl cyclase

MB has direct inhibitory effects on nitric oxide synthases (NOS), both constitutive and inducible [23, 24] and blocks accumulation of cyclic guanosine monophosphate (cGMP) by inhibiting the enzyme guanylate cyclase [23]. MB blocks the activity of nitric oxide (NO)-dependent guanylate cyclase via the oxidation of the active haemo centre [23] or by inactivation of its haemo-deficient apoenzyme [24]. Data suggest that MB is a more specific and potent inhibitor of NOS than guanylyl cyclase, because direct NO-donating compounds in the presence of MB can still partially activate c-GMP signaling pathways [25, 26]. Hence, MB restores vascular reactivity to endogenous catecholamines [27] in the setting of excessive NO production, but has no intrinsic contractile property, as shown in experimental conditions [28]. The effect of MB is due to NO inhibition (effect of NO on K<sub>Ca</sub> channels), although there are presently no data on the relative inhibition of the NOS isoforms by MB, nor is there any information on regional organ differences in the inhibition of cNOS.

### Antioxidant effects of MB

MB possesses unique biochemical properties that are the attributes of a neuroprotective agent, such as being a powerful antioxidant. MB blocks the iron-containing enzymes [29] such as xanthine oxidase an iron containing enzyme that is inhibited by methylene blue due to a competition with molecular oxygen for xanthine derived electrons [30]. MB protects organs from the toxic effects of free oxygen radicals by competing with molecular oxygen for the transfer of electrons by XO and is effective in attenuating ischemia-reperfusion syndrome [31, 32].

Methylene blue is permeable through biomembranes and it readily crosses the blood-brain barrier and selectively stains brain tissue [33]. It has been demonstrated that after administration MB is selectively trapped in the brain and its concentrations are 10-20 times higher in the brain than in circulation one hour after administration [33]. MB has affinity for tissue oxidases, so it concentrates in mitochondria where is able to maintain mitochondrial function by accepting electrons from blocked components of the respiratory chain and by transferring them to cytochrome oxidase or oxygen, improving mitochondrial respiration [34]. The effects of MB are reflected in increased activity in processes coupled with mitochondrial energy production such as Na/K ATPase activity and intermediary metabolism [35]. For this reason, MB constitutes a metabolic enhancer that accelerates the activity of the electron transport chain. The intracerebroventricular administration of MB has been shown to reduce the minimum alveolar anaesthetic concentration (MAC) of volatile anaesthetics [36] and the intravenous administration reduced the anaesthetic requirement of propofol [37].

### MB and platelets aggregation

MB inhibits the arachidonic acid metabolism in human blood platelets [38]. When human platelets are incubated with MB that oxidizes cellular NADPH, a marked inhibition of platelet aggregation and of the metabolism of the arachidonic acid in both the cyclooxygenase and lipoxygenase pathway is found. Thus, MB possesses inhibitory effects on platelet activation, adhesion and aggregation [39] synergistically with an inhibition of platelet thromboxane A<sub>2</sub> and endothelial prostacyclin I<sub>2</sub> (PGI-2) production [40, 41].

## Methylene blue in cardiac arrest and cardiopulmonary resuscitation

Ischemic brain injury after cardiac arrest (CA) is still one of the major causes of failure to achieve survival in patients experiencing a cardiac arrest; only approximately 5% survive. Although survival rates are increasing with 32–34°C hypothermia during the first 24 h after a CA [42], complete neurologic recovery is often far from certain, and brain injury is the cause of death in 68% of patients after out-of-hospital CA and 23% after in-hospital CA [43].

Some pilot animal experiments indicated that MB could possibly be advantageous for use in experimental cardiac arrest and cardiopulmonary resuscitation (CPR), as it seemed both to stabilize the systemic circulation and decrease the risk for insufficient arterial blood pressure after restoration of spontaneous circulation (ROSC) [44]. Our porcine model of 20 min experimental cardiac arrest [44] explored the central nervous effects of global ischemia, the pathophysiology leading to neurological damage, and possibilities for enhancing neurological function after cardiac arrest.

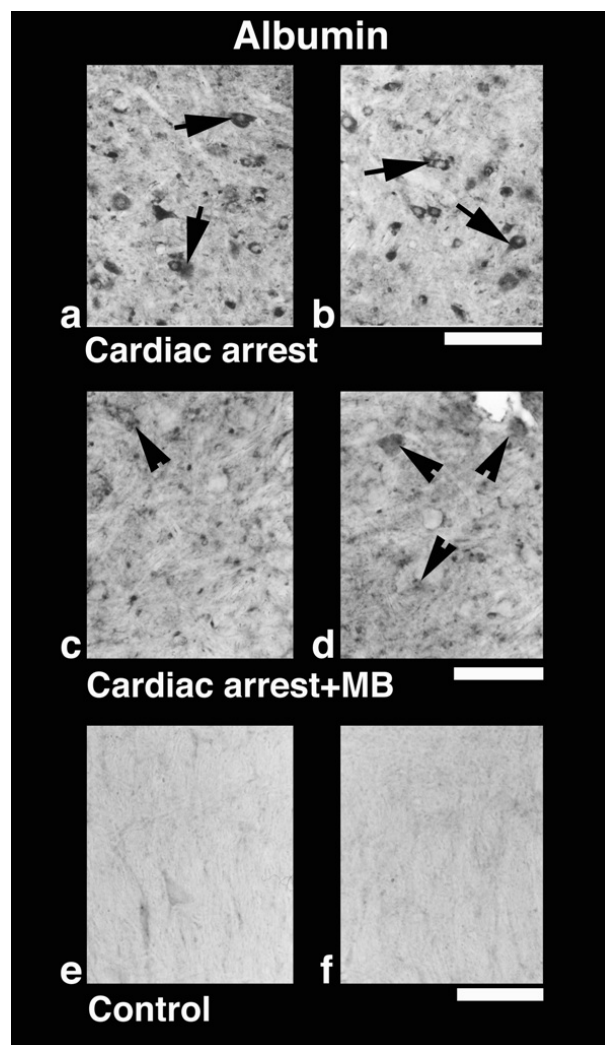
### *Methylene blue and neuroprotection*

Endogenous albumin immunostaining to detect leakage across the BBB is a well-standardized method in neuropathological laboratories and has been used by several authors in the past [45] to determine BBB disruptions. MB administration during CPR and the initial phase after ROSC reduced the blood-brain barrier disruptions and neurologic injury considerably, but did not, on the other hand, reverse the ongoing detrimental process (Fig. 2).

Other nitric oxide synthase inhibitors (NOS inhibitors) such as the non-selective NOS inhibitor N<sup>G</sup>-methyl-L-arginine (L-NAME) [46], N<sup>G</sup>-nitro-L-arginine (L-NNA) [47] and selective inhibitors such as aminoguanidine (iNOS inhibitor), 1-(2-(trifluoromethylphenyl)imidazol) (TRIM), a nNOS inhibitor, were also tested in experimental models of cardiac arrest [47, 48]. Schleien et al [46] demonstrated that non-specific NOS inhibition with L-NAME attenuated the post-ischemic cerebral and myocardial hyperemia.

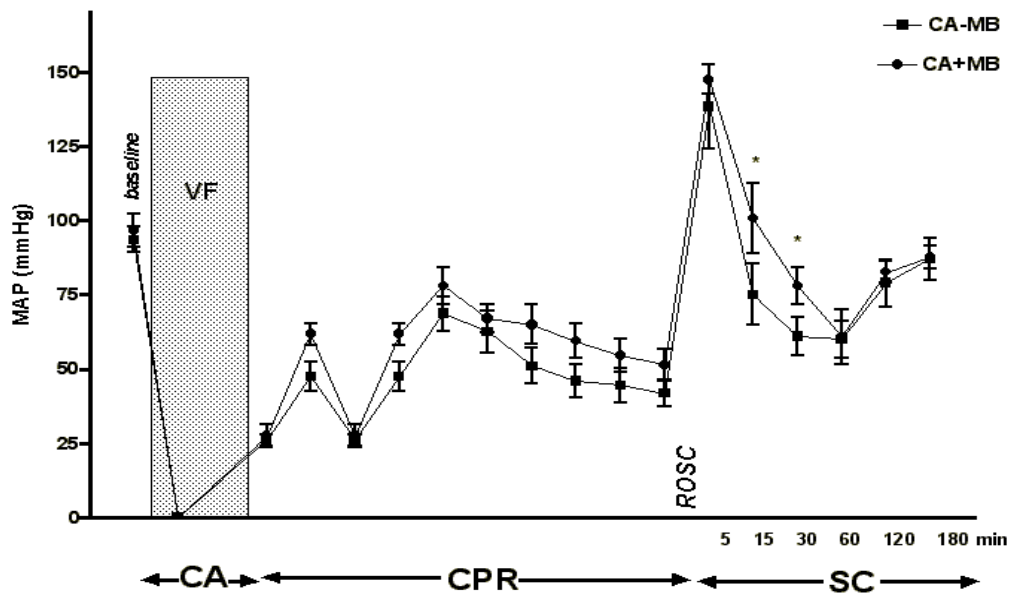
### *Methylene blue and survival in cardiac arrest*

In our porcine model continuously administered MB and hypertonic saline with dextran during CPR, and continued for 50 min after ROSC, increased short-term (4-hr) survival in comparison with the group receiving normal saline during the course of this experiment. In addition, the group that received MB (MB group) showed less hypotension and better cardiac performance and coronary perfusion pressure initially after return of spontaneous circulation and showed fewer signs of cerebral and cardiac injury [49]. Zhang et al [50] studied non-selective inhibition of NOS with



**Fig. 2.** Representative examples of albumin immunoreactivity in the cerebral cortex (parietal a, c, e and temporal b, d, f) following cardiac arrest without CPR in the CA group (e, f), with CPR without treatment with methylene blue (arrows; a, b), cardiac arrest with MB (arrowheads; c, d). Marked albumin immunoreactivity is seen in the cortical neurons (arrows) after cardiac arrest and CPR without MB.

L-NNA in a swine resuscitation model, demonstrating that pre-arrest NOS inhibition did not improve survival, but reduced requirements for epinephrine and closed-chest compression. Adams et al [47] suggested that an intact basal neuronal NOS (nNOS) activity is vital for survival after ischemia/reperfusion injury and that inducible NOS (iNOS) inhibition prior to ischemia reperfusion protects myocardial function after ROSC. Using a method of endothelial stimulation to produce endothelial derived NO (periodic acceleration pGz), superior myocardial function post-resuscitation was demonstrated [48], possibly indicating that complete endothelial NOS (eNOS) inhibition during CA is deleterious to cardiac function in resuscitation from CA. Hence, it was also considered that the beneficial



**Fig. 3.** Mean arterial pressure. The group treated with methylene blue (CA + MB) represented with black circles and the group without MB (CA-MB) denoted with black squares. Significant differences ( $*p < 0.01$ ) between groups were seen at 15 and 30 minutes after return of spontaneous circulation (ROSC). CA-cardiac arrest; CPR cardiopulmonary resuscitation

effects of non-selective inhibitors were limited, because they inhibit eNOS to a similar degree and may therefore aggravate effects of cardiac and brain ischemia. In comparison with these NOS inhibitors it must be mentioned that MB interferes with several pathways and it may be that the protective effects of MB in ischemia/reperfusion injury are not only explained by the inhibition of nitric oxide production. MB administration attenuated morphologic changes suggesting that NO and consequent peroxynitrite formation during ischemia-reperfusion injury contributes to cerebral injury.

#### *Methylene blue and hemodynamics*

MB not only increased short-term survival after CA and CPR as compared to a control group given normal saline, but also induced less hypotension (Fig.3), better coronary pressure and cardiac performance early after ROSC, thus improving post-resuscitation hemodynamics. In the same paper [49], MB decreased myocardial injury as assessed by troponin I, probably due to an improvement in coronary perfusion pressure initially after ROSC. It has previously been demonstrated that nonselective inhibition of NO by NG monomethyl-L-arginine increases coronary blood flow after ischemia, thus improving contractility [50]. NO affects myocardial contraction in a dose-dependent fashion, with low doses of NO resulting in positive inotropic effects and higher concentrations exerting negative inotropic effects [51]. Resuscitation studies using hypertonic-

hyperoncotic solutions have usually reported an improvement in myocardial blood flow during CPR [52] as a result of improved microcirculation during ischemia [53], whereas only minor effects have been found during recirculation.

The present results unequivocally demonstrate that MB administration during CPR reduced BBB disruption and subsequent neurologic injury after ischemia-reperfusion from CA and improved early hemodynamics and survival rates in a porcine model of cardiac arrest. Therefore, this approach should be worthy of testing in human cerebral ischemia and reperfusion after CA.

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## Albastru de metilen – medicament vechi cu indicații noi?

### Rezumat

Tocmai când am început după mai bine de un secol să înțelegem utilizarea clinică a albastrului de metilen, vechile sale proprietăți încep să fie din nou descrise și, ca urmare, apar noi posibile indicații. Oxidul nitric stimulează guanilat ciclaza, care transformă guanozin trifosfatul în ciclic guanozin monofosfat (cGMP). Ca urmare a creșterii cGMP se produce o cascadă a enzimelor protein kinase cu relaxare pe musculatura netedă și vasodilatație. Albastrul de metilen (MB) posedă efecte inhibitorii directe asupra enzimelor care au rol în sinteza oxidului nitric și blochează acumularea de cGMP. De asemenea, MB blochează enzimele care conțin fier, cum ar fi xantin oxidaza, și în consecință are efecte antioxidante. Datorită acestor acțiuni, se descriu noi indicații ale MB, precum sindromul vasoplegic după bypass-ul cardiopulmonar la om și stopul cardiac la animale.

**Cuvinte cheie:** albastru de metilen, leziune oxidativă, neuroprotecție, hemodinamică, resuscitare cardiopulmonară