

Utilization of methylene blue in the setting of hypotension associated with concurrent renal and hepatic failure: A concise review

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ABSTRACT

Renal failure, hepatic failure and hepatorenal syndrome can be associated with clinically significant hypotension, a clinical state often referred to as vasoplegia or vasoplegic syndrome. Vasoplegia is thought to be related to dysregulation of endothelial homeostasis and subsequent endothelial dysfunction due to direct and indirect effects of various inflammatory mediators. Vasoplegia has been observed in all age groups and in various clinical settings, including sepsis, hemorrhagic shock, hemodialysis, and cardiac surgery. Among mechanisms thought to be contributory to vasoplegic syndrome, the nitric oxide/cyclic guanosine monophosphate pathway appears to play a prominent role. Methylene blue, an inhibitor of nitric oxide synthase and guanylate cyclase, has been found to improve the hypotension associated with various clinical states. Evidence also suggests that methylene blue may be effective in improving systemic hemodynamics and vasoplegia associated with hepatic failure. We describe two cases of vasoplegia associated with concurrent hepatic and renal failure – both demonstrating a favorable hemodynamic response to methylene blue without apparent side effects. A review of methylene blue use in the setting of hepatic and renal failure then follows.

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INTRODUCTION

Systemic inflammatory response associated with profound vasodilation, known as vasoplegia or vasoplegic syndrome (VS), has been observed in various clinical settings. The classic description of VS includes hypotension, low systemic vascular resistance and increased requirement for intravenous fluid and vasopressor administration.¹⁻² Vasoplegia has been associated with cardiopulmonary bypass (CPB), severe sepsis, anaphylaxis and hemodialysis.²⁻⁵ Episodic and persistent hypotension has also been described in chronic liver disease.⁶⁻⁷

Vasoplegic syndrome has been observed in all age groups.⁸⁻⁹ The incidence of VS varies, but can reach 10% in post-cardiac surgery patients and may be as high as 42% following left ventricular assist device placement for end-stage heart failure.^{2, 10-11} Vasoplegia may be present in up to 50% of patients who die from sepsis and has been observed in association with anaphylaxis and protamine administration for reversal of systemic heparinization.^{3, 5, 12-16}

There is evidence that methylene blue (MB), an inhibitor of the vasodilatory effects of nitric oxide (NO) and other nitrovasodilators on endothelium and vascular smooth muscle, may be therapeutically beneficial in vasoplegia. It may be that dysfunction of a common pathophysiologic effector pathway is responsible for vasoplegia attributable to various clinical states, and that MB might be helpful in the treatment of hypotension mediated by this pathway.^{1-2, 4-5, 17} There is also evidence that MB may be effective in improving systemic hemodynamics in vasoplegia associated with chronic liver disease.^{6, 18}

This review discusses the administration of MB in the setting of simultaneous hepatic and renal failure. Special emphasis is placed on potential risks and benefits of MB therapy in this clinical setting. In addition, we present two illustrative cases of persistent hypotension in the setting of concurrent renal and hepatic failure, both with favorable hemodynamic responses to methylene blue.

ILLUSTRATIVE CASE #1

A 56-year-old male with history of morbid obesity, hypertension, non-alcoholic steatohepatitis (NASH), type II diabetes, and renal insufficiency developed severe panniculitis complicated by gram-positive bacteremia and sepsis. Despite aggressive antimicrobial therapy, surgical debridement, and hemodynamic support, the patient developed multi-organ dysfunction, including pulmonary failure, renal failure, and progressive hepatic failure (encephalopathy and coagulopathy).

Shortly after recovering from the initial infection, the patient experienced an episode of gram-negative bacteremia and sepsis. Despite recovery from the latter episode, the patient's renal failure worsened and he became dialysis-dependent. At that time, he also underwent tracheostomy and percutaneous endoscopic gastrostomy (PEG) tube placement.

Approximately two weeks later, the patient began experiencing recurrent episodes of hypotension. These hypotensive episodes initially responded to intermittent vasopressor administration and intravenous fluid therapy, with transient responses to stress-dose hydrocortisone replacement therapy. However, he progressively deteriorated, requiring continuous vasopressor administration and escalating intravenous fluid boluses. His laboratory and radiographic (computed tomography, abdominal ultrasound) findings repeatedly failed to reveal an infectious source. Diagnosis of concurrent hepatic and renal failure was made due to worsening hepatic function parameters (total bilirubin 3.6 mg/dL, INR of 1.9) with clinically apparent jaundice and encephalopathy. Of note, broad-spectrum antibiotics were administered during each of the above episodes, with planned re-adjustment or discontinuation of antibiotic therapy based on microbiology

culture and sensitivity data. Because of the continued requirement for large-volume intravenous fluid resuscitation and vasopressors, a trial dose of methylene blue was administered in hopes of liberating the patient from vasopressors.

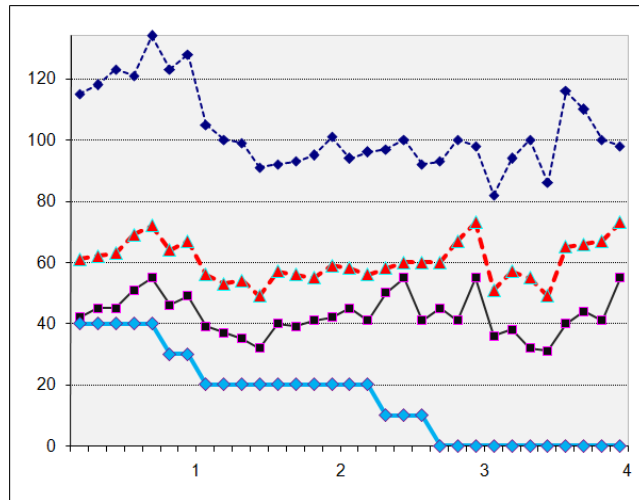


Figure 1. Graphical representation of blood pressure and norepinephrine infusion rate following the initial administration of methylene blue in *patient #1*. The X-axis shows time in hours. Systolic blood pressure (*dashed diamond line*), mean arterial pressure (*dashed triangle line*), and diastolic blood pressure (*solid square line*) are represented in mmHg on the Y-axis. Please note that the values of the norepinephrine infusion rate on the graph (*solid diamond line*, mcg/min) are multiplied by 10 (i.e., 40 mcg/min on the graph represents an actual infusion rate of 4 mcg/min).

After a single intravenous dose of MB (1 mg/kg diluted in 100 mL of Dextrose 5% in water [D5W], administered over 1 hour), the patient’s norepinephrine infusion was weaned over a period of four hours, followed by discontinuation of vasopressin infusion (**Figure 1**). He returned to baseline blood pressure for a period of 12 hours. At that time, the patient experienced another episode of hypotension and an additional dose of MB (0.5 mg/kg in 100 mL D5W) was administered. Following the second dose of MB, the patient’s blood pressure improved again, and he remained normotensive for an additional 96 hours. Note that the patient’s central venous pressure also gradually increased following MB administration (**Figure 2**). The patient’s arterial oxygen saturation remained unchanged during both MB infusions (range, 97% to 100%). No side effects were noted during MB use.

ILLUSTRATIVE CASE #2

A 62-year-old male with end stage liver disease due to NASH and known hepatorenal syndrome presented to the emergency department complaining of chest pain and abdominal discomfort. He was noted to have significantly increased abdominal girth despite undergoing paracenteses approximately every four days for difficult-to-treat ascites. The patient also complained of increasing generalized edema and significant weight gain over the past several weeks. He denied any fevers, chills, nausea, vomiting or diarrhea. His medical history was also significant for type I diabetes, thrombocytopenia, and recently diagnosed stage IV adenocarcinoma of the lung (making him ineligible for combined hepatic-renal transplantation).

On admission, he was found to be hypotensive, with blood

pressure of 58/40 mmHg (baseline blood pressure approximately 70/50 mmHg). He was afebrile, with a heart rate of 83 beats/minute and respiratory rate of 20 breaths/minute. The patient was cachectic and appeared to be in mild distress. His chest examination revealed bibasilar rales. His abdomen was distended, mildly tender, with shifting dullness. There was no rebound, guarding or focal peritonitis. The remainder of his physical examination was normal.

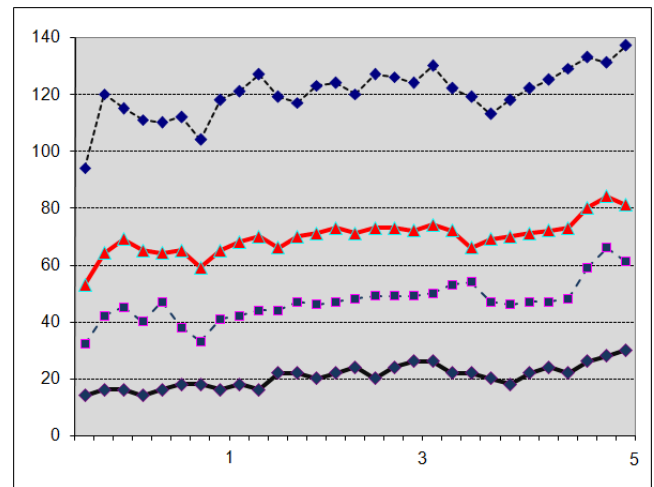


Figure 2. Graphical representation of blood pressure and central venous pressure following the second administration of methylene blue in *patient #1*. The X-axis shows time in hours. Systolic blood pressure (*dashed diamond line*), mean arterial pressure (*solid triangle line*), and diastolic blood pressure (*dashed square line*) are represented in mmHg on the Y-axis. Note the gradual increase in central venous pressure (*solid diamond line*) from 14 mmHg to 28 mmHg over the 5-hour period following methylene blue administration.

Initial laboratory studies included sodium 125 mmol/L (normal 136-145); chloride 92 mmol/L (normal 100-108); blood urea nitrogen (BUN) 25 mg/dL (normal 5-25); creatinine 4.8 mg/dL (normal 0.5-1.4); phosphorus 4.4 mg/dL (normal 2.3-4.1); lactic acid 4.8 mmol/L (normal 0.3-2.1); albumin 2.4 g/dL (normal 3.5-5.0), and INR 1.54. Chest radiogram demonstrated bibasilar atelectasis. Electrocardiogram showed normal sinus rhythm.

The patient was admitted to the intensive care unit, where he remained hypotensive (systolic blood pressure [SBP] between 70 and 80 mmHg) despite adequate fluid resuscitation by both invasive (central venous pressure of 10-12 mmHg) and noninvasive criteria (essentially normal echocardiogram). He was also noted to have hypotension-related lightheadedness and somnolence. At this point, norepinephrine infusion was added to treat the vasoplegic state, and titrated to maintain mean arterial pressure \geq 60 mmHg. Despite otherwise unremarkable workup, the patient remained norepinephrine-dependent for ten subsequent days (SBP between 75 and 100 mmHg).

The patient underwent numerous diagnostic tests to help establish the cause of his hypotension. Echocardiography demonstrated normal left ventricular function and ejection fraction (70%). Computer tomography of the abdomen and pelvis demonstrated moderate ascites, for which the patient was already undergoing serial paracenteses with periprocedural volume replacement using 25% albumin solution. Ascitic fluid, blood and urine cultures showed no bacterial growth. The patient underwent scheduled

hemodialysis sessions three times a week. He remained afebrile during this period.

After ten days of continued norepinephrine dependence, the patient was given intravenous methylene blue (1 mg/kg in D5W) in order to help facilitate the weaning of the norepinephrine drip. A slow, but sustained and reproducible response to MB was noted (**Figure 3**). The patient was subsequently placed on an oral regimen of MB (1 mg/kg) given twice daily, with equally reliable responses. After liberation from norepinephrine drip and transfer to the general medical ward, the patient was discharged from the hospital on continued twice daily oral MB regimen. No side effects were noted during MB therapy in this patient.

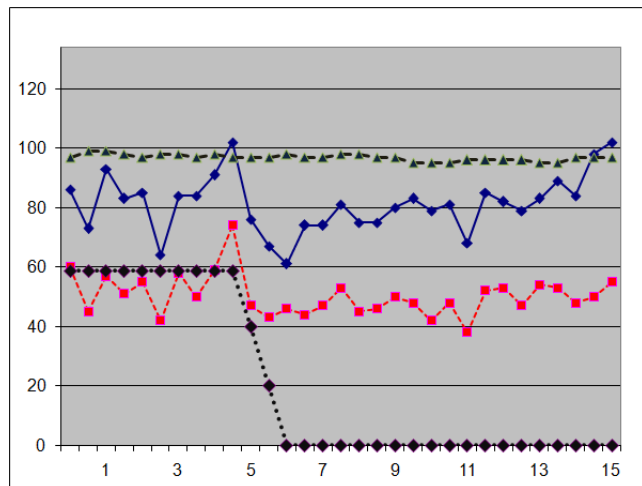


Figure 3. Graphical representation of blood oxygen saturation, blood pressure and norepinephrine infusion rate following the initial administration of methylene blue in *patient #2*. The X-axis shows time in hours. Systolic blood pressure (*solid diamond line*), diastolic blood pressure (*dashed square line*) are represented in mmHg on the Y-axis. Arterial oxygen saturation is represented by the *dashed triangle line*. Please note that the values of the norepinephrine infusion rate on the graph (*dotted diamond line*, mcg/min) are multiplied by 10 (i.e., 60 mcg/min on the graph represents an actual infusion rate of 6 mcg/min).

DISCUSSION

Vasoplegia or vasoplegic syndrome (VS) is a state of endothelial dysregulation resulting in persistent hypotension despite adequate fluid resuscitation and vasopressor administration. While different definitions have been proposed for VS in the setting of cardiac surgery and sepsis, there are no formalized definitions for vasoplegia associated with other conditions, such as anaphylaxis, renal or hepatic failure.^{3, 19-21}

There is evidence to suggest that MB may be effective in improving systemic hemodynamics in the setting of vasoplegia related to chronic liver disease, hepatopulmonary and hepatorenal syndromes.^{6, 18} This report describes two cases of vasoplegia in the setting of simultaneous hepatic and renal failure – both associated with favorable hemodynamic response to MB administration. A focused review of MB use in the setting of hepatic and renal failure then follows.

VASOPLEGIC SYNDROME: RISK FACTORS AND PATHOPHYSIOLOGY

Numerous potential risk factors for VS have been identified. In cardiac surgery, independent risk factors for postoperative

vasoplegia include preoperative intravenous heparin use, angiotensin-converting enzyme inhibitor use, and calcium channel blocker use.^{17, 22-23} While the incidence of VS among patients with these predisposing factors varies, it is important to be aware of these clinical associations.² With anaphylactic shock, refractory vasoplegia is encountered in relatively few cases, with no clearly defined risk factors.²⁴ In the setting of septic shock, the vasoplegic response may or may not depend on adequate source control, but may be based on how advanced is the underlying pathophysiologic process. While the search continues for more precise determination of risk factors for VS in different clinical settings, significant evidence exists to support the presence of a common physiologic pathway that leads to vasoplegia.

Normal physiologic response to an injurious stimulus is usually self-limited and commensurate to the magnitude of that stimulus. In more severe cases, the response may inappropriately persist, progressing through the spectrum of severe systemic inflammatory response syndrome (SIRS), multiorgan dysfunction (MOD), multiorgan failure (MOF) and ultimately, death.¹⁹ One of the most important manifestations of severe SIRS is circulatory failure with low systemic vascular resistance (SVR), low mean arterial pressure (MAP), systemic hypoperfusion and tissue malperfusion.¹ The physiologic response of SIRS appears to be mediated by: (a) various neurotransmitters (including acetylcholine, adenosine triphosphate (ATP) and substance P); (b) factors responsible for hemostasis (including adenosine diphosphate (ADP), serotonin, bradykinin and thrombin); as well as (c) biologic amines (including norepinephrine and histamine).¹ These mediators, in turn, induce the synthesis of two endothelial autotoxins – endothelium derived relaxing factor (EDRF or nitric oxide) and prostacyclin (PGI₂) – resulting in vasoplegia.¹ Vasoplegia due to non-septic mechanisms can be thought of as a type of “pure” form of SIRS, including VS associated with cardiopulmonary bypass, hemodialysis, or hepatic failure.^{2, 6, 25}

Regardless of the initial etiology, VS appears to represent a dysregulation of NO synthesis/release and vascular smooth muscle cell guanylate cyclase (GC) activation. Nitric oxide is produced by two types of NO synthase (NOS) relevant to this review – a constitutive endothelial (eNOS) type and an inducible (iNOS) type.² Upregulation of iNOS and increased NO production lead to generation of cyclic guanosine 3'-5' monophosphate (cGMP), with resultant hypotension.²⁶ NO-dependent pathways also participate in the pathophysiology of hypotension following hemorrhagic shock and post-cardiac arrest states.²⁷⁻²⁸ Vasoplegic syndrome has been attributed to a combination of endothelial injury, arginine-vasopressin system dysfunction, and release of other vasodilatory inflammatory mediators, including tumor necrosis factor alpha (TNF- α) and interferon gamma (IFN- γ).²⁹⁻³² Elevated interleukin-1 (IL-1) levels in inflammatory states can also promote vasodilation through increasing the levels of intracellular cGMP (**Figure 4**).²

The pathophysiologic changes of VS are thought to be due to actions induced by nitric oxide (NO) production from L-arginine by a family of NO synthases (NOS).²⁶ A *de novo* synthesis of iNOS takes place under the influence of proinflammatory cytokines and/or endotoxin in the heart, the lungs, and the vascular smooth muscle cells.^{2, 33-34} Subsequently, NO stimulates soluble guanylate cyclase (sGC) which, in turn, generates cyclic guanosine 3'-5' monophosphate (cGMP). This leads to smooth muscle cell cGMP-mediated vasodilation and decreased myocyte contractility, including relaxation of myocardial and vascular

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smooth muscle.^{5, 21, 32, 35-36} Additional harmful effects of iNOS-produced NO include impaired gas exchange, vascular leakage, and multi-organ failure.^{21, 33-34, 37-39} In contrast, the constitutive eNOS produces minute amounts of NO, maintaining basal regional vascular tone and blood flow.³⁴

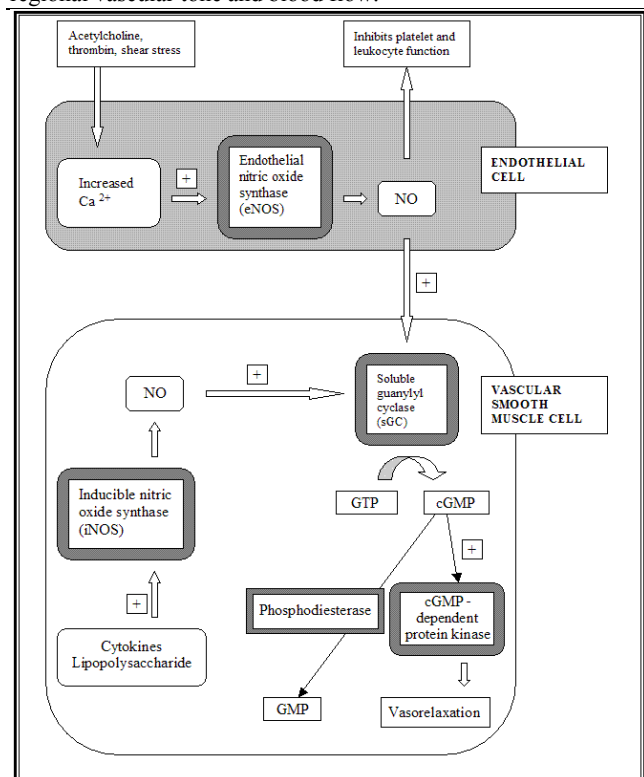


Figure 4. Schematic representation of NO/cGMP-dependent pathways. Note the endothelial (eNOS) and inducible (iNOS) isoforms of the nitric oxide synthase and their associated functional steps.

METHYLENE BLUE: THE MOLECULE AND ITS PHARMACOLOGY

Methylene blue USP (3,7-dipropylphenothiazine chloride and 3,7-dipropylphenothiazine chloride trihydrate, molecular formula $C_{16}H_{18}ClN_3S \cdot 3H_2O$, **Figure 5**) has a molecular weight of 371.923 and consists of dark green crystals that turn to deep blue color when dissolved in water or alcohol. It is approved for oral or intravenous administration in the setting of methemoglobinemia (especially following topical benzocaine use), hemolysis, and as a surgical ‘tracer’ dye for detection of fluid leaks (mainly from gastrointestinal and urinary systems).⁴⁰⁻⁴¹ Methylene blue (MB) is available as a solution (10 mg/mL) and is usually administered enterally or intravenously. Oral absorption ranges from 53% to 97%.² The onset of the hemodynamic effects of MB is relatively rapid.² Of interest, intratracheal MB administration has been described experimentally.⁴³

Methylene blue readily enters the erythrocyte, and at low concentrations is reduced to leucomethylene blue (**Figure 6**). MB is eliminated in bile, feces, and urine as leucomethylene blue.⁴¹⁻⁴² At higher doses, MB itself becomes an oxidant, and in the presence of excess MB or a defect in the methemoglobin reduction mechanisms, the dye accumulates and functions as a

hemoglobin oxidizing agent, resulting in hemolysis, methemoglobinemia, and hyperbilirubinemia.⁴¹

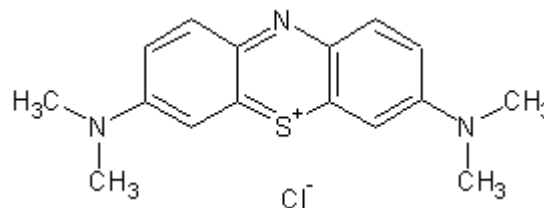


Figure 5. Chemical structure of methylene blue.

Methylene blue has been used in patients of all age groups.⁸⁻⁹ Overall, the recommended safe oral dose of MB appears to be between 1-2 mg/kg and 3-4 mg/kg, depending on source.^{41, 44} Methylene blue lacks sulfonic acid groups and does not bind to plasma proteins.⁴⁵ Methylene blue (MB) is a soluble guanylyl cyclase (sGC) inhibitor that blocks sGC action in vascular smooth muscle, scavenges NO and inhibits NO synthesis.^{24, 46-48}

Methylene blue seems to counteract the effects of NO and other nitrovasodilators in endothelium and vascular smooth muscle and is believed to act competitively with NO.⁴⁹ By binding to the iron heme-moiety of the soluble guanylyl cyclase (sGC) and blocking sGC action in vascular smooth muscle, NO decreases the levels of cGMP and alleviates the vasorelaxant effect seen in VS.^{10, 24, 50-52} A single dose of intravenous MB (1-2 mg/kg with 20-minute infusion time) has been used as a ‘rescue’ treatment in the setting of vasoplegia of anaphylaxis and cardiac surgery.^{17, 53-54} In pediatrics, MB has been used as adjunctive medical therapy in severe sepsis and acquired methemoglobinemia, with recommended doses of 1-2 mg/kg for a full-term infant.⁴¹

Continuous MB infusion has been described in patients who do not respond to a single dose of MB, and has been administered for variable lengths of time (120 mg of MB diluted in D5W, given continuously from 1 to 6 hours).^{2, 54} Escalating doses of MB infusion have also been used.⁵⁵ Several reports describe administration of MB intraoperatively during cardio-pulmonary bypass (CPB) to treat vasoplegia.^{36, 56} In one report, MB was added to the pump prime as a treatment of vasoplegia associated with septic endocarditis during a valve operation, and followed postoperatively as an infusion.³⁶ In another report, CPB was re-instituted due to norepinephrine-refractory protamine reaction, with improvement noted only after MB infusion.⁵⁶

Methylene blue has been used in oncology for sentinel lymph node detection⁵⁷, in treatment of methemoglobinemia complicating topical benzocaine use (MB hastens the conversion of methemoglobin to hemoglobin)^{8,44}, congenital methemoglobinemia⁵⁸, priapism⁵⁹, neonatal hypotension⁶⁰, as an anti-malarial agent⁶¹, and in the setting of vasoplegia related to cardiac surgery, sepsis, anaphylaxis, liver failure and hemodialysis.^{2, 4, 13-14, 25, 62-63}

METHYLENE BLUE: SIDE EFFECTS AND CONTRAINDICATIONS

Methylene blue should not be used in patients with documented hypersensitivity to this drug. Although contraindicated in severe renal insufficiency, MB has been used safely in hemodialysis-dependent patients.^{2, 25} Methylene blue should be used cautiously in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and low levels of endogenous NADPH (essential to the

production of leucomethylene) because of the risk of a Heinz body hemolytic anemia.⁶⁴ Methylene blue can also exacerbate dapsone-induced hemolytic anemia because of the formation of dapsone-reactive metabolite hydroxylamine, which oxidizes hemoglobin.⁶⁵⁻⁶⁶ Pathway steps relevant to these phenomena are outlined in Figure 7.

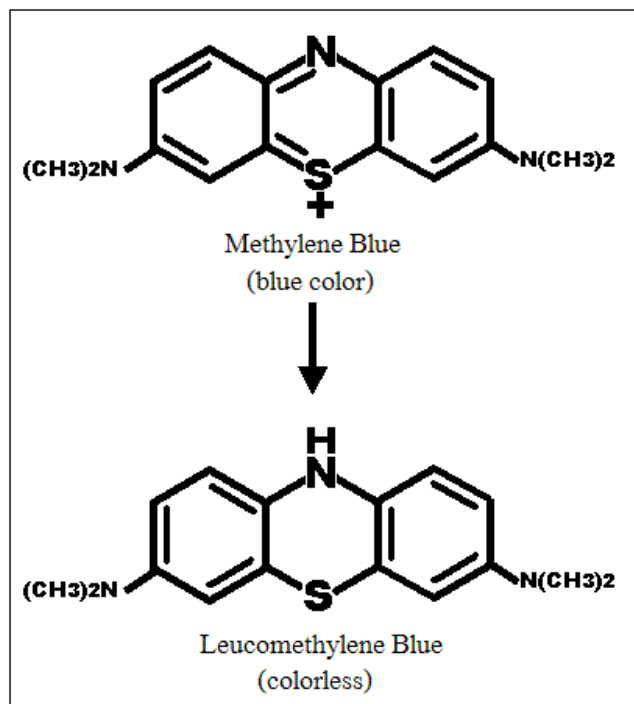


Figure 6. Reduction of methylene blue to leucomethylene blue.

A number of side effects have been described in association with MB use. Although rare, adverse reactions to intravenous MB include cardiac arrhythmias (transient nodal rhythm and ventricular ectopy), coronary vasoconstriction, angina, decreased cardiac output, decreased renal blood flow, reduced mesenteric blood flow, increases in pulmonary vascular resistance and worsening gas exchange.^{18-19,48,56} Arrhythmias and precordial pain associated with MB administration are usually transient and self-limiting.²

Adverse reactions have also been noted after oral administration of MB.² In the neonatal population, enteral administration of more than 2 mg/kg of MB has been reported to result in severe methemoglobinemia and hemolysis.⁴¹ Use of MB has been associated with Heinz body hemolytic anemia and hyperbilirubinemia after intraamniotic injections and oral administration in the pediatric patient.^{44, 67}

Methylene blue is reduced in the erythrocyte to leucomethylene blue, and is excreted primarily in the urine as leucomethylene blue and MB.⁶⁸ Hemolytic anemia, Heinz body anemia, and hyperbilirubinemia have been reported with MB doses exceeding 2 mg/kg.⁶⁷ Anemia associated with MB usually manifests itself within 24 hours of injection, and can be seen up to 12 days after MB use.⁴⁴ The timing of anemia and hyperbilirubinemia complicating MB administration are similar, with the bilirubin peak at approximately 4 days after use and the anemia peak at approximately 5 days.⁴⁴

Most side effects of MB appear to be dose-dependent and do not occur with doses <2 mg/kg.⁶⁹⁻⁷⁰ Most studies report normal renal function and pulmonary gas exchange (expressed as the ratio of PaO₂ to inspired oxygen fraction) following MB administration. Transient and self-limiting elevations in serum aspartate aminotransferase and alanine aminotransferase have been reported in one study, although it is not clear whether these elevations were due to MB, concurrent administration of norepinephrine, or both.²⁰ In one series, five patients who received preoperative intravenous MB infusion (3-5 mg/kg MB in 500 mL of normal saline) for localization of parathyroid adenomas, developed self-limiting postoperative encephalopathy.⁷¹ It was noted that the common factors in all five cases of encephalopathy were: (a) female gender of the patients and (b) preoperative use of serotonin-metabolism modifying agents.⁷¹

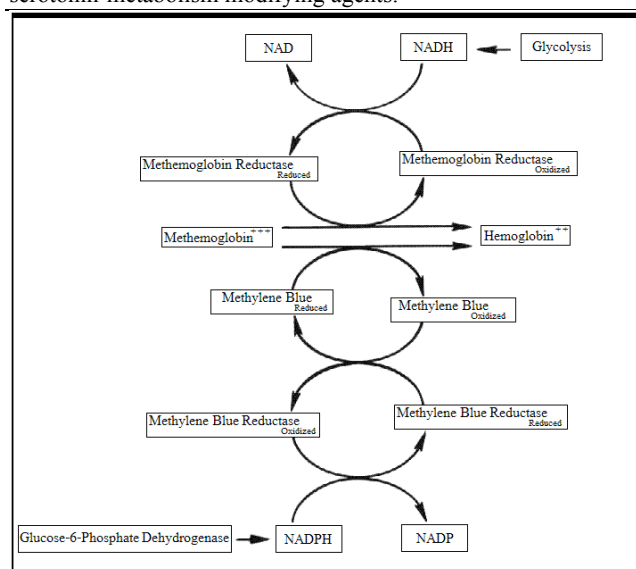


Figure 7. Outline of important steps involved in the metabolism of methylene blue.

Methylene blue is known to turn urine greenish-blue.^{20, 72} This benign discoloration can be alarming to patients, although it is self-limiting and disappears 1-2 days after discontinuing the drug. Mild skin discoloration can occur, but is also self-limiting, and can be treated with administration of dilute hypochlorite solution.⁴²

Other reported side effects associated with MB include confusion, headache, fever, nausea, vomiting, abdominal pain and diaphoresis.² Subcutaneous and intradermal injections of MB have been reported to cause necrotic abscesses.^{2, 73} A rare but devastating photosensitivity epithelial desquamation has been reported in infants undergoing phototherapy after receiving MB.⁷⁴⁻⁷⁵ This serious reaction has been attributed to breakdown of lysosomal membranes after interacting with light in the presence of the photosensitizing MB.⁷⁴⁻⁷⁵ Anaphylactic reactions have been known to occur, although rarely, following MB administration.⁷⁶ Of note, MB interferes with the pulse oximeter's light emission (wavelength of ~660 nm), resulting in falsely depressed oxygen saturation readings.⁷⁷

METHYLENE BLUE USE IN VASOPLEGIA OF RENAL AND HEPATIC FAILURE

There are very few reports of MB use in the setting of hemodialysis, renal and/or hepatic failure. The rationale for MB use in vasoplegia associated with hemodialysis/renal failure and hepatic failure is based on the fact that NO and iNOS are known to play a role in these clinical states.^{6-7, 62} It has long been postulated that antagonists of nitric oxide and NO production may prevent hypotension associated with both hepatic and renal failure.^{25, 78}

Hypotension is one of the most common complications encountered during hemodialysis.²⁵ Although fluid removal and relative hypovolemia during dialysis can contribute to transient hypotension, many patients without hypovolemia experience moderate to severe hypotensive episodes during hemodialysis.⁷⁹⁻⁸⁰ This phenomenon is thought to be related to intra-dialysis nitric oxide elevations, leading to significant and relatively rapid vasodilation.^{25, 81-82} In the setting of hemodialysis-associated vasoplegia, MB has been shown to be effective in preventing hypotension when given as a bolus of 1 mg/kg body weight followed by an infusion at 0.1 mg/kg for 210 minutes on dialysis days and as a bolus-only on non-dialysis days.²⁵ In the current study, both patients were dialysis-dependent. However, their hypotension did not appear to be associated with hemodialysis. In **illustrative case #1**, the patient was initially receiving continuous renal replacement therapy and was later transitioned to intermittent hemodialysis. No clinical differences in patient hemodynamic status were noted between these two modes of renal support. In **illustrative case #2**, the patient was undergoing scheduled hemodialysis sessions, with no apparent decline in blood pressure during dialysis sessions.

Hepatic failure is often complicated by hypotension, low systemic vascular resistance, and reduced sensitivity to vasoconstrictor drugs.⁷ This state is similar to the vasoplegia associated with sepsis and endotoxic shock, and has been reproduced in humans by injection of endotoxin.⁸³⁻⁸⁴ Moreover, plasma concentrations of endotoxins are known to be elevated in hepatic cirrhosis.⁸⁵ While increased endogenous production of nitric oxide has been proposed as a mediator of peripheral arterial vasodilation and hyperdynamic circulatory changes in cirrhosis, decreased intrahepatic NO production has been suggested as one of the contributing factors to portal hypertension.⁸⁶⁻⁸⁷ Of note, up to 15% of patients with cirrhosis develop hepatopulmonary syndrome⁸⁸ and it is estimated that up to 40% of patients with cirrhosis and ascites will develop hepatorenal syndrome within five years of the onset of their disease.⁸⁹

The use of methylene blue has not been widely reported in the setting of hepatorenal syndrome. One study examined the effects of MB on renal function, portal and systemic hemodynamics in cirrhotic patients with ascites.⁸⁷ In that study, methylene blue was administered at 3 mg/kg (MB in 100 mL D5W, infused over a 20-minute period). There were no significant differences in mean arterial pressure, heart rate, cardiac output, systemic vascular resistance, plasma active renin, and portal vein velocities between methylene blue and placebo.⁸⁷ However, urinary sodium excretion, fractional excretion of sodium and serum nitric oxide levels were all significantly decreased four hours after MB administration, and returned to baseline over an additional four hour period.⁸⁷

Table 1. Clinical studies of methylene blue in the setting of hepatic and/or renal failure.

Author (ref) and year	Clinical setting	Major results/findings
Schenk Ref 6 2000	A case series (n = 7) describing the effect of MB on patients with hepatopulmonary syndrome. Methylene blue (3 mg/kg) given intravenously over a 15-minute period.	Intravenous methylene blue improved hypoxemia and hyperdynamic circulation in patients with hepatic cirrhosis and hepatopulmonary syndrome. There was a significant increase in P _a O ₂ , mean pulmonary artery pressure, and pulmonary vascular resistance following MB administration. Cardiac output decreased and systemic vascular resistance increased following MB. No significant side effects were noted, except blue-green discoloration of urine for approximately 1-2 days.
Peer Ref 25 2001	Investigational study of MB administration in hemodialysis patients. Study based on the fact that plasma NO levels have been found to be elevated in hemodialysis (HD) patients, likely contributing to HD-associated hypotension. (n = 41, 18 HD patients with hypotension, 18 HD patients without hypotension, and 5 healthy controls). Methylene blue was given as a bolus of 1 mg/kg followed by a constant infusion of 0.1 mg/kg for 210 minutes until the end of HD session. On non-dialysis days, only the bolus dose was given.	In hypotension-prone patients, MB completely prevented the hypotension during dialysis and increased both systolic and diastolic blood pressure on non-dialysis days. The generation of nitrates was significantly higher in the hypotensive group than in the normotensive group. In normotensive patients, MB increased blood pressure during the first hour of dialysis and during the first 90 minutes on non-dialysis days. The blood pressure in healthy controls remained unchanged. No side effects were noted.
Kalambokis Ref 87 2005	Investigational study of MB administration on renal, portal, and systemic hemodynamics in patients with cirrhosis and ascites (n = 20). Methylene blue (3 mg/kg) was administered to the experimental group (n = 10). Placebo was given to the control group (n = 10).	Mean arterial pressure, heart rate, cardiac output, systemic vascular resistance, plasma reactive renin, plasma aldosterone and antidiuretic hormone, serum urea, serum creatinine, serum sodium, urinary flow rate, glomerular filtration rate, effective renal plasma flow, portal flow volume, and portal vein velocity were not modified by MB or placebo. Urinary sodium excretion, fractional sodium excretion and serum NO levels were significantly decreased 4 hours after MB administration, but returned to basal levels over an additional 4-hour period.
Almeida Ref 18 2007	Case report (n = 1) of MB use in a patient with hepatopulmonary syndrome.	Administration of MB in the setting of hepatopulmonary syndrome with a large right to left intrapulmonary shunt resulted in significant improvements in vascular tone and the hyperdynamic circulation, but was reproducibly and reversibly associated with worsening hypoxemia.

Another NOS inhibitor, L-NMMA, was found to impair renal hemodynamics and function despite being able to improve overall systemic hemodynamics.⁹⁰⁻⁹¹ Given these findings, along with its overall side effect profile, MB administration may be contraindicated in patients with hepatorenal syndrome-associated vasoplegia who are not expected to need long-term hemodialysis. On the other hand, in the setting of long-term renal replacement therapy, MB use to improve systemic hemodynamics may be indicated, especially if it leads to significant improvement in patient quality of life, much like in **illustrative case #2**, where the patient was able to be discharged from the hospital on oral MB therapy. In the current report, both patients showed favorable hemodynamic responses to MB administration and were able to come off continuous vasopressor therapy. It is unclear whether effects due to hepatic and/or renal failure were primarily responsible for vasoplegia observed in both cases. However, our

observations suggest that MB may indeed be effective in improving systemic hemodynamics in the setting of hypotension associated with simultaneous hepatic-renal failure.

Reports of methylene blue use in the setting of hepatopulmonary syndrome demonstrate beneficial effects of MB on vascular tone and hyperdynamic circulatory changes in patients with hepatic cirrhosis.^{6,18} However, there is conflicting evidence with regards to the effect of MB on oxygenation in the setting of hepatopulmonary syndrome.^{6,18} While Schenk *et al* report that MB improves hypoxemia in this setting⁶, others observed reproducible and reversible worsening of hypoxemia in association with MB use in patients with hepatopulmonary syndrome and right-to-left intrapulmonary shunting.¹⁸ Thus, NO-cGMP pathway inhibitors must be used with extreme caution in patients with hepatopulmonary syndrome and right to left intrapulmonary shunting until more evidence is available to support this practice.¹⁸ None of the patients in the current report had hepatopulmonary syndrome, and we did not note any apparent change in patient oxygenation following methylene blue administration.

CONCLUSIONS

Although much has been learned about MB and its applications in the setting of vasoplegia, many questions remain. Administration of MB in patients with VS increases blood pressure and systemic vascular resistance, and decreases vasopressor administration requirements. We presented a review of MB use in the setting of hepatic and renal failure and two illustrative cases of vasoplegia associated with simultaneous hepatic and renal failure, both of which demonstrated favorable hemodynamic response to MB, with no apparent side effects. Future studies of MB in the setting of hepatic and/or renal failure will need to be conducted in multi-institutional, prospective, blinded, and randomized fashion, and will need to be designed to answer specific clinical questions with sufficient statistical power. Until such studies are available, the use of MB in these clinical settings should be considered very carefully, with full knowledge of indications, contraindications, and potential side effects of this drug.

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