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Serotonin Syndrome Following Methylene Blue Administration During Cardiothoracic Surgery

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Abstract

Introduction: Despite its favorable safety profile, there have been reports of methylene blue-induced encephalopathy and serotonin syndrome in patients undergoing parathyroidectomy. We report a case of serotonin syndrome following methylene blue administration in a cardiothoracic surgery patient. *Case Report:* A 59-year-old woman taking preoperative venlafaxine and trazodone was given a single dose of 2 mg/kg methylene blue (167 mg) during a planned coronary artery bypass and mitral valve repair. Postoperatively, she was febrile to 38.7°C and developed full-body tremors, rhythmic twitching of the perioral muscles, slow conjugate roving eye movements, and spontaneous movements of the upper extremities. Electroencephalography revealed generalized diffuse slowing consistent with toxic encephalopathy, and a computed tomography scan showed no acute process. The patient's symptoms were most consistent with a methylene blue-induced serotonin syndrome. Her motor symptoms resolved within 48 hours and she was eventually discharged home. *Discussion:* Only 2 cases of methylene blue-induced serotonin syndrome during cardiothoracic surgery have been described in the literature, with this report representing the third case. Methylene blue and its metabolite, azure B, are potent, reversible inhibitors of monoamine oxidase A which is responsible for serotonin metabolism. Concomitant administration of methylene blue with serotonin-modulating agents may precipitate serotonin syndrome.

Keywords

cardiology, serotonin syndrome, methylene blue, encephalopathy, cardiothoracic surgery, cardiology

Introduction

Vasoplegic syndrome (VS) is a form of vasodilatory shock manifesting as reduced systemic vascular resistance, high or normal cardiac output, and significant hypotension.[1] Commonly reported in the cardiothoracic surgery literature, VS occurs in 5% to 25% of patients who require cardiopulmonary bypass (CPB) and up to 40% of patients undergoing left ventricular assist device placement.[1,2] Development of VS predicts poor outcomes including prolonged hospital and intensive care unit (ICU) lengths of stay and increased mortality.[3,4]

Mechanistically, CPB produces a proinflammatory state where cytokines and endotoxins increase the expression of inducible nitric oxide synthase (iNOS). Elevations in iNOS upregulate nitric oxide production which increases the conversion of guanosine triphosphate to cyclic guanosine monophosphate (cGMP) via guanylate cyclase. cGMP blocks calcium from entering smooth muscle cells leading to relaxation and vasodilation.[5] Additional risk factors for VS include left ventricular ejection fraction (LVEF) <35% and perioperative medications including beta-blockers, heparin, and angiotensin-converting enzyme (ACE) inhibitors.[3,4,6]

Traditionally, treatment of VS has involved the administration of fluids and vasoactive agents. Although efficacious in a number of patients, fluids and vasopressors do not always correct hypotension.[7,8] Treatment of the underlying etiology with methylene blue (MB) has become increasingly common because it may improve outcomes in VS, including mortality.[8-11] MB inhibits guanylate cyclase activity which reduces cGMP concentrations and increases intracellular calcium leading to vascular responsiveness.[5]

Despite its favorable safety profile, MB has recently been implicated in precipitating serotonin syndrome and encephalopathy in patients undergoing parathyroidectomy.[12-14] To our knowledge, only 2 case reports describing central nervous

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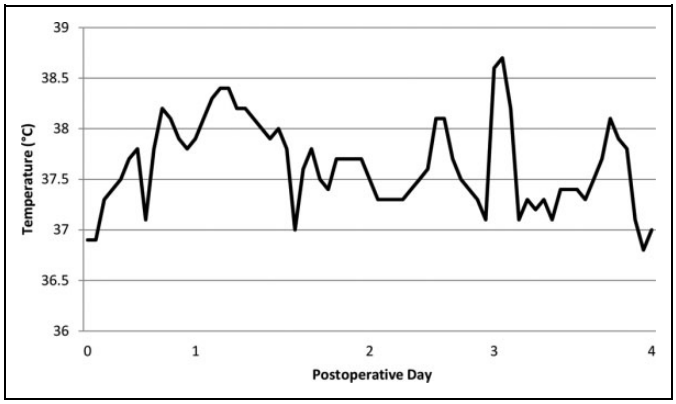

Figure 1. Temperature trend in degrees Celsius following methylene blue exposure.

system toxicity following MB administration exist in the cardiothoracic surgery literature.[15,16] We report a third case in a female who underwent coronary artery bypass and mitral valve repair.

Case Report

A 59-year-old female was admitted following 1 week of worsening shortness of breath and lower extremity edema. Her psychiatric history included borderline personality disorder, depression, and anxiety for which she took venlafaxine 100 mg twice daily and trazodone 100 mg daily as needed. On admission, venlafaxine was changed from 100 mg twice daily to 225 mg once daily using an extended-release (ER) formulation for ease of administration. Her height was 152 cm and her weight was 77.5 kg.

An echocardiogram (ECHO) revealed left ventricular systolic and diastolic dysfunction with an LVEF of 35% to 45%, consistent with congestive heart failure New York Heart Association Class III Stage D. Cardiac catheterization uncovered severe, nonischemic cardiomyopathy, mitral regurgitation, and a high grade, proximal, right coronary artery (RCA) lesion. A coronary artery bypass graft (CABG) and mitral valve repair were scheduled 2 weeks after admission. Her heart failure was medically managed until then and included the initiation of lisinopril 5 mg daily. Her venlafaxine dose was reduced to 187.5 mg daily due to an acute kidney injury. She received a dose of trazodone 100 mg the day before surgery.

Mitral valve repair was completed with a papillary muscle sling using a 3.5-mm Gore-Tex® shunt and placement of a 24-mm Physio-II Annuloplasty Ring®. Reversed saphenous vein grafting from the aorta to the distal RCA was used during her on-pump CABG. Clamp time lasted 87 minutes with a total perfusion time of 127 minutes. Intraoperative hypotension was managed with intermittent phenylephrine boluses and a single dose of MB 167 mg (2 mg/kg) due to preoperative lisinopril administration. An intra-aortic balloon pump was inserted and she was transferred to the cardiothoracic ICU on mechanical ventilation.

Eight hours after receiving MB, the patient developed full-body tremors, rhythmic twitching of the perioral muscles, slow conjugate roving eye movements, and spontaneous movements of the upper extremities. Vital signs at that time included a heart rate of 117 beats per minute, a blood pressure of 88/67 mm Hg, and a respiratory rate of 26 breaths per minute. Her highest temperature was 38.7°C and is trended in Figure 1. Laboratory values at this time and throughout her stay are summarized in Table 1.

An electroencephalogram (EEG) revealed generalized, diffuse slowing consistent with toxic encephalopathy, infection, or degenerative disease. No epileptiform discharges were identified. Blood, urine, and sputum cultures at the time were negative. Lorazepam 1 mg intravenously (IV) and levetiracetam 1000 mg IV every 12 hours were given with modest effect. Cyproheptadine was not administered. The patient's symptoms were most consistent with MB-induced serotonin syndrome.

On postoperative day 1, the patient was febrile to 38.4°C with bilateral clonus and rigidity, decerebrate posturing, and nystagmus. Sedation was maintained with a continuous infusion of midazolam 1 to 5 mg/h and fentanyl 12.5 to 75 mcg/h. Her intra-aortic balloon pump was removed on this day. On postoperative day 2, the patient was extubated with no further evidence of facial twitching or clonus. Reintubation became necessary on postoperative day 3 due to hypoxia. A computed tomography (CT) scan of her head at this time revealed a normal brain with no cause for unresponsiveness identified.

The patient was eventually extubated for a second time on postoperative day 6. Following extubation, she was agitated and unable to follow commands but did not exhibit symptoms of serotonin syndrome. Her cognitive dysfunction slowly resolved over the next week. On postoperative day 14, her venlafaxine was reinitiated at 37.5 mg daily which was titrated up over 4 days to 225 mg daily and she was eventually discharged home.

Discussion

MB is a tricyclic phenothiazine that was first used as a therapeutic agent to treat malaria in 1891.[17] Its chemical structure has served as the precursor for tricyclic antidepressants, antimalarials, and antipsychotics. Recently, MB has been employed as a staining agent during parathyroidectomy,[12] as an antidote for methemoglobinemia,[18] and to correct hypotension in septic shock.[19] In addition, MB is being increasingly used during cardiothoracic surgery to mitigate VS.[9,11]

The efficacy of MB in cardiothoracic surgery has been evaluated in the preoperative, intraoperative, and postoperative setting with few adverse effects reported.[8,10,11] The most common adverse effects in these studies included increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and blue–green discoloration of the urine and skin. MB as an IV bolus (2 mg/kg) followed by a stepwise infusion up to 2 mg/kg/h in patients with septic shock infrequently reduced platelet count and lowered body temperature.[19] Overall, adverse effects in these trials were rare, but most were not adequately powered to assess them.

Table 1. Laboratory Values Throughout Hospitalization.[a]

	Admit	Hospital day 7	Preop	POD 0	POD 1	POD 2	POD 3	POD 5	Discharge
Sodium, mEq/L	138	137	135	139	139	139	142	145	138
Potassium, mEq/L	3.7	3.5	5.0	4.1	4.5	4.6	4.6	3.5	4.5
Chloride, mEq/L	97	93	102	109	104	104	105	100	100
Carbon dioxide, mEq/L	31	31	23	17	20	23	22	35	27
BUN, mg/dL	20	38	30	23	23	20	22	20	23
Creatinine, mg/dL	0.98	1.34	1.50	1.19	1.44	1.24	1.24	1.16	1.13
Glucose, mg/dL	252	106	120	154	140	92	108	153	115
Calcium, mg/dL	8.9	9.3	9.2	6.8	8.1	7.4	8.1	8.5	9.7
WBC, $\times 10^3/\mu L$	14.4	17.6	13.3	44.7	25.8	16.3	20.5	10.4	15.6
Platelets, $\times 10^3/\mu L$	368	447	371	242	227	129	143	162	504
Hemoglobin, g/dL	11.3	13.2	10.4	9.6	8.6	6.1	8.0	7.7	11.4
Hematocrit, %	35.5	40.9	33.5	30.2	26.2	19.3	25.6	24.7	36.0
Alkaline phosphatase, U/L	163					95	560		
AST, U/L	48					52	268		
ALT, U/L	51					14	143		
Creatinine kinase, U/L				707	1093	781	628		

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Preop, preoperative; POD, postoperative day; WBC, white blood cell.
[a]Documented laboratory values for the patient from admission through discharge by hospital day.

MB-induced serotonin syndrome and encephalopathy has been well described after parathyroidectomy in patients who were taking serotonin-modulating agents including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs).[12-14] Patients typically exhibited encephalopathy with confusion, agitation, delirium, hallucinations, speech abnormalities, vision loss, unfocused gaze, blurred vision, and seizures. Interestingly, only 2 cases of MB-induced neurotoxicity have been reported in patients undergoing cardiothoracic surgery, despite a similar dosing strategy (Table 2).

The first case involved a 60-year-old male who underwent heart transplantation.[15] He had a history of depression for which he was taking trazodone 100 mg at bedtime and escitalopram 20 mg daily. During surgery, the patient developed refractory hypotension and subsequently received a 1 mg/kg bolus of MB followed by a continuous infusion of 0.5 mg/kg/h. Postoperatively, the patient experienced delayed recovery from anesthesia and a temperature of 40°C, ocular clonus, mydriasis, lateral nystagmus, myoclonic jerks, shivering, and hypertonicity. A CT scan of the head showed no acute pathology and an EEG revealed slowing of electrocerebral function consistent with encephalopathy due to toxic, metabolic, or pharmacologic changes. The patient was sedated with midazolam and intubated for 24 hours to allow for the clearance of MB. Neurologic manifestations resolved in 48 hours and the patient was discharged.

The second case occurred in a 49-year-old female undergoing mitral valve replacement. She had a history of anxiety and depression for which she was taking paroxetine 40 mg daily.[16] Intraoperative refractory hypotension eventually required the administration of 2 doses of MB at 1 mg/kg. Postoperatively, the patient awoke agitated and confused and was febrile to 40°C with myoclonic jerks, shivering, hypertonicity, dilated pupils, hypereflexia, and muscle rigidity. A head CT and magnetic resonance imaging (MRI) revealed no acute pathology and an EEG showed disturbances of electrocerebral function consistent with a toxic encephalopathy. The patient was treated with a loading dose of 12 mg of cyproheptadine, followed by 2 mg every 2 hours for the next 48 hours. Neurological manifestations improved over the course of a week and she was eventually discharged home.

Our patient was a 59-year-old female undergoing a CABG and mitral valve repair with a history of a personality disorder, anxiety, and depression treated with venlafaxine 100 mg twice daily, which was changed to 225 mg ER once daily on admission and trazodone 100 mg daily as needed. During surgery, vasoactive-refractory hypotension eventually required the administration of a single dose of MB at 2 mg/kg (167 mg). This dose was similar to the mg/kg bolus doses reported in the other 2 cases. Physical examination findings in our patient were also similar to the other reports. The degree of hyperpyrexia our patient experienced was not as severe as the other cases (38.7°C vs 40°C). Our patient met the definition for serotonin syndrome based on the Hunter Serotonin Toxicity Criteria.[20] The Naranjo probability scale indicated that MB-induced serotonin syndrome was possible (score = 3) in our patient and was not reported in the other 2 cases.[15,16,21]

MB-induced serotonin syndrome is likely due to the drug's ability to act as a potent, reversible monoamine oxidase A (MAO-A) inhibitor which blocks serotonin breakdown. Clinical doses of MB have been shown to completely inhibit MAO-A and partially inhibit MAO-B.[22] In humans, MB is metabolized to yield 2 bioactive metabolites, azure B, the major metabolite, and azure A. In vitro studies have shown that azure B is a 5 to 10 times more potent inhibitor of MAO-A compared to MB indicating azure B may be responsible for inducing serotonin syndrome and encephalopathy.[23]

This case report is not without limitations. Our patient had a significant history of mental illness which could have

Table 2. Case Reports of Methylene Blue-Induced Serotonin Syndrome During Cardiothoracic Surgery.[a]

Case	Type of surgery	Methylene blue dose	Serotonin-modulating medications	Symptoms	Peak laboratory values	Imaging
Grubb et al[15]	Cardiac transplant	1 mg/kg bolus followed by 0.5 mg/kg/h continuous infusion (total dose unknown)	Escitalopram 20 mg daily; trazodone 100 mg daily	Ocular clonus; mydriasis; lateral nystagmus; myoclonic jerks; shivering; hypertonicity; hypoxia; temp 40°C	WBC 18.39 × 10^{-9} k/μL; creatinine 3.3 mg/dL; K 5.1 mEq/L; CPK 1406 U/L	Head CT: no acute pathology. EEG: electrocerebral function slowing consistent with encephalopathy due to toxic, metabolic, or pharmacologic changes
Shanmugam et al[16]	Mitral value replacement	1 mg/kg × 2 doses (total dose unknown)	Quetiapine 25 mg twice daily; paroxetine 40 mg daily	Myoclonic jerks; fine tremors of extremities; mydriasis; hypereflexia; shivering; hypertonicity; agitation; temp 40°C; HR 110 BPM; BP 170/100 mm Hg	WBC 23.2 × 10^{-9} k/μL; creatinine 2.5 mg/dL; K 7.1 mEq/L; CPK 3734 U/L; ALT 3594 U/L; LDH 5494 U/L; amylase 514 U/L; troponin 2.14 μg/L; urine myoglobin 5460 U/L	Brain CT and MRI: no acute pathology. EEG: electrocerebral disturbances consistent with toxic encephalopathy
Current case	CABG and mitral valve repair	2 mg/kg × 1 dose (167 mg)	Venlafaxine 225 mg daily; trazodone 100 mg daily PRN (received 100 mg day prior to surgery)	Bilateral clonus; rigidity; full-body tremors; rhythmic twitching of perioral muscles; slow conjugate roving eye movements; nystagmus; decerebrated posturing; spontaneous movements of upper extremities; altered mental status; temp 38.4°C; HR 117 BPM; BP 88/67 mm Hg	WBC 44.7 × 10^{-9} k/μL; creatinine 1.5 mg/dL; K 5 mEq/L; CPK 1093 U/L; ALT 206 U/L	Head CT: no acute pathology. EEG: generalized diffuse slowing consistent with toxic encephalopathy, infection or degenerative disease

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; BPM, beats per minute; CABG, coronary artery bypass graft; CPK, creatine kinase; CT, computed tomography; EEG, electroencephalogram; HR, heart rate; LDH, lactate dehydogenase; MRI, magnetic resonance imaging; WBC, white blood cell; PRN, as needed.

[a]A brief summary of the 3 cases of reported methylene blue-induced serotonin syndrome during cardiothoracic surgery (2 previous cases and this current case).

contributed to her agitation. In addition, withholding her psychoactive medications for an extended period could have contributed to her slow cognitive recovery. Besides this, the patient was sedated with fentanyl which has been implicated in precipitating serotonin syndrome and could have contributed to her prolonged symptoms.[24] We did not rechallenge the patient because additional MB was not clinically warranted. Finally, serotonin syndrome is a subjective, clinical diagnosis that is difficult to distinguish from postoperative encephalopathy.[25]

Conclusions

We report a third case of MB-induced serotonin syndrome in a patient undergoing cardiothoracic surgery. Identifying patients at high risk of VS who are taking serotonin-modulating agents prior to cardiothoracic surgery is a reasonable approach to preventing MB-induced serotonin syndrome but this strategy has not been validated. The nonspecific presentation of MB-induced serotonin syndrome necessitates a broad differential including malignant hyperthermia, neuroleptic malignant syndrome, anesthesia-induced emergence agitation, and postoperative encephalopathy. Management is largely supportive and symptom driven as the reaction dissipates over time. A greater awareness of the potential interaction between MB and serotonergic agents is necessary in order to better identify patients at risk, validate preventive strategies, develop management regimens, and anticipate patient outcomes.

Declaration of Conflicting Interests

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