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Perioperative Diagnosis and Treatment of Serotonin Syndrome Following Administration of Methylene Blue

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

E James Francescangeli
E Sonia Vaida
E Anthony S. Bonavia

Department of Anesthesiology and Perioperative Medicine, Penn State Milton S. Hershey Medical Center, Hershey, PA, U.S.A.

Corresponding Author: Anthony Bonavia, e-mail: abonavia@hmc.psu.edu
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Patient: Male, 67
Final Diagnosis: Serotonin syndrome
Symptoms: Agitation • muscular spasticity, deficient muscular control • nystygmus • sweating • tachycardia
Medication: Methylene Blue
Clinical Procedure: Total abdominal colectomy
Specialty: Anesthesiology

Objective: Unusual clinical course

Background: Serotonin syndrome (SS) involves serotonergic hyperactivity caused by excessive activation of 5-HT2A receptors. As the use of antidepressants increases, so does the population of patients at risk for developing this complication. The diagnosis is made based on current serotonergic medication use in conjunction with certain clinical signs. The severity of the clinical presentation may vary, especially when the complication occurs while the patient is under general anesthesia. As a result, the incidence of SS is likely underreported and treatment may be delayed, leading to life-threatening complications.

Case Report: A 67-year-old, American Society of Anesthesiologist physical status 3 male with multiple medical comorbidities, including anxiety/depression and chronic neck pain, presented for an elective laparoscopic total abdominal colectomy for colonic inertia. His intraoperative course was significant for SS likely triggered by the administration of methylene blue, which only became clinically apparent during anesthetic emergence. We considered and systematically ruled out other potential causes of his clinical condition. His management was primarily supportive, using hydration and benzodiazepine administration, and resulted in full neurologic recovery.

Conclusions: SS is an underdiagnosed condition with limited treatment options beyond symptom management. Thus, vigilance, early diagnosis, and cessation of offending medications are of utmost importance. Anesthesiologists managing at-risk surgical patients must have a high clinical suspicion of perioperative SS if their patients exhibit tachycardia, hypertension, and hyperthermia together with clonus, agitation, diaphoresis, or hypertonia. These signs may be masked by general anesthesia and may only manifest themselves upon anesthetic emergence.

MeSH Keywords: Drug-Related Side Effects and Adverse Reactions • Methylene Blue • Serotonin Syndrome

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Background

Serotonin syndrome is a potentially life-threatening condition characterized by serotonergic hyperactivity. Its clinical manifestations vary widely, although it often involves autonomic hyperactivity, mental status changes, and neuromuscular changes. Because of the spectrum of symptoms and their severity, the true incidence of serotonin syndrome is unknown [1].

Serotonin toxicity is caused by excessive synaptic activation of 5-HT2A receptors, often by increasing the extracellular concentration of serotonin. This may be done by blocking its extracellular clearance (by using selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], or monoamine oxidase inhibitors [MAOIs]) or by increasing its release from serotonergic neurons (with methylenedioxymethamphetamine and fenfluramine) [2]. Methylene blue, which is often used intraoperatively for diagnostic purposes, is also a potent MAOI. Although SSRIs and SNRIs do not usually precipitate serotonin syndrome when used in isolation, adding a single dose of MAOI, such as methylene blue, can precipitate this condition if used in conjunction with the former medications.

Making a perioperative diagnosis of serotonin syndrome is often challenging because of the effects of general anesthesia, the multitude of drugs that the patient receives in the perioperative period, and the broad differential diagnosis for the condition [3]. Furthermore, physical examination signs such as muscle rigidity and myoclonus may be masked or difficult to detect in a paralyzed patient who is surgically draped on the operating room table.

Case Report

A 67-year-old, 90-kg, American Society of Anesthesiologists physical status 3, white male with a history of hypertension, renal cell carcinoma status post right partial nephrectomy, chronic neck pain, anxiety/depression, and colonic inertia presented for an elective laparoscopic total abdominal colectomy with ileorectal anastomosis under general anesthesia. His medication history is summarized in Table 1. His surgical history was remarkable for C4–C6 anterior discectomy with cervical fusion and placement of a neurostimulator 2 years earlier. The patient's wife had deactivated the neurostimulator before this surgery, per physician instruction. She also stated that the patient had been experiencing occasional flushing, diaphoresis, and fevers for 4 months before this surgery, although this had not been worked up further. Trazodone and tramadol were added to the patient's regimen of duloxetine 6 months before this surgery. His anesthetic history was notable for agitation and combative behavior upon anesthetic emergence from his cervical discectomy procedure.

General anesthesia was induced with 2 mg/kg propofol, 1 mcg/kg fentanyl, and 1 mg/kg lidocaine. After ensuring adequate bag-mask ventilation, 50 mg rocuronium was administered, followed by oral endotracheal intubation. Anesthesia was maintained using approximately 1 MAC sevoflurane. Pain control was achieved using preoperative bilateral transversus abdominis plane blocks, as well as administration of fentanyl 250 mcg, hydromorphone 0.6 mg, and acetaminophen 1 g intraoperatively. Surgery progressed unremarkably until approximately 2 hours after induction when methylene blue was administered to confirm the structural integrity of the ureters. Following administration of the dye, surgeons noted significant muscle tension and requested additional muscle paralysis, despite zero twitches on facial nerve train-of-four (TOF) stimulation. After completion of the procedure, stimulation of the ulnar nerve produced 4 twitches with fade and the patient was given 5 mg neostigmine and 1 mg glycopyrrolate for reversal of neuromuscular blockade.

The patient experienced prolonged anesthetic emergence that lasted approximately 20 minutes beyond complete elimination

Table 1. Summary of patient's medical history.

Medical diagnosis	Treatment
Hypertension	Hydrochlorothiazide
Renal cell carcinoma	Right partial nephrectomy
Chronic neck pain	C4–C6 anterior discectomy and cervical fusion Neurostimulator placement Tramadol
Anxiety/depression	Alprazolam, duloxetine
Colonic inertia	Simethicone, docusate, lubiprostone, polyethylene glycol
Gastroesophageal reflux disease	Ranitidine
Hyperlipidemia	Simvastatin, aspirin

Table 2. Hunter serotonin toxicity criteria. For any patient with a concern for serotonin syndrome, a serotonergic medication must be present as well as 1 of the primary symptoms. Except in the case of spontaneous clonus, all primary symptoms will need an additional secondary symptom to confirm the diagnosis of serotonin syndrome.

Presence of a serotonergic agent	Presence of primary symptom	Secondary symptom if necessary	Diagnosis confirmed by criteria
Present	Spontaneous clonus		Yes
Present	Inducible clonus	Agitation *or* diaphoresis	Yes
Present	Ocular clonus	Agitation *or* diaphoresis	Yes
Present	Tremor	Hyperreflexia	Yes
Present	Hypertonic *and* Temperature >38°C	Ocular clonus *or* inducible clonus	Yes

of expired sevoflurane. Ulnar nerve TOF monitoring confirmed 4 strong and equal twitches. Although the patient's pupils were noted to be of normal caliber, 0.4 mg naloxone was administered in divided doses to rule out occult opioid overdose as the cause of prolonged emergence. The patient subsequently opened his eyes, although he remained very lethargic and unable to follow commands. During emergence, upper extremity muscle rigidity, ocular clonus, and athetosis of the eyebrows were noted. The patient remained afebrile but tachycardic. He was extubated approximately 30 minutes after paralytic reversal, and after confirming spontaneous ventilation with adequate minute ventilation. He then recovered in the postanesthesia care unit (PACU), where his neurostimulator was reactivated.

The patient's postoperative course was notable for persistent tachycardia, ocular nystagmus, and upper- and lower-extremity muscle rigidity. He was also agitated and diaphoretic with flushed skin. On examination, rhythmic myoclonic activity was observed upon his attempt to grasp objects. He also demonstrated spontaneous clonus of his lower extremities, lip-smacking, and uncontrolled tongue movements. Based on observations of the patient and the use of the Hunter serotonin toxicity criteria, a diagnosis of serotonin toxicity was made [4]. Opioids and serotonergic agents were withheld, as was the patient's home medications of trazodone, tramadol, and duloxetine. In the PACU, the patient received intravenous fluids and 1 mg midazolam, which reduced his heart rate and agitation. The patient was subsequently admitted to the surgical intensive care unit for overnight observation. Though agitated, he remained aphasic with flat affect and masklike facial expression. A computed tomography noncontrast scan of the head was performed to rule out any acute intracranial process, but the results were grossly unremarkable.

Within 24 hours, the patient's mental status improved and he was able to communicate, although he remained lethargic with slow and purposeful mentation. He was transferred to a regular nursing floor after 24 hours in the intensive care unit. He recovered appropriately from a surgical standpoint and was discharged home 4 days after surgery.

Discussion

Given the increasing incidence of clinical depression and the use of serotonergic medications for its treatment, one may assume that the population of patients at risk for developing perioperative serotonin syndrome is increasing [1,5]. Thus, the importance of identifying patients at risk for serotonin syndrome before anesthetic induction is of utmost importance and will likely determine the patient's perioperative outcome.

Early suspicion, correct diagnosis, and initiation of treatment and monitoring are essential to preventing autonomic instability and death from serotonin syndrome [6,7]. The diagnosis is purely clinical and possible differential diagnoses include neuroleptic malignant syndrome, malignant hyperthermia, and anticholinergic delirium. Various diagnostic criteria for serotonin syndrome have been proposed, and the Hunter Serotonin Toxicity Criteria are the most widely accepted (sensitivity of 84%, specificity of 97%) [4]. Table 2 summarizes the diagnostic criteria of serotonin toxicity [4].

These criteria are difficult to apply in patients undergoing general anesthesia. In fact, our patient only exhibited ocular clonus, agitation, diaphoresis, and spontaneous clonus postoperatively. Retrospectively, this patient's delayed emergence may have offered evidence of SS, but definitive diagnosis was delayed until more specific symptoms were noted. Crystalloids and benzodiazepines were initiated to treat serotonin syndrome. Neuroleptic malignant syndrome was considered less likely due to the acute onset of symptoms and the lack of administration of neuroleptic medications [6]. Malignant hyperthermia was also deemed unlikely because of the absence of fever, hypercarbia, or metabolic acidosis [6]. Unlike neuroleptic malignant syndrome, anticholinergic toxicity, and malignant

hyperthermia, the major distinguishing features of serotonin syndrome are the presence of neuromuscular excitation, including hyperreflexia, clonus, and myoclonus [3].

In our clinical scenario, the patient's reported symptoms of flushing, diaphoresis, and fevers preoperatively may have been related to his home regimen of trazodone (a serotonin antagonist and reuptake inhibitor), tramadol (a serotonin and norepinephrine reuptake inhibitor), and duloxetine (a serotonin-norepinephrine reuptake inhibitor). A recently documented case report described a diagnosis of SS secondary to the use of tramadol and citalopram in a patient who presented to an emergency department with altered mental status and spontaneous clonus [8]. The addition of fentanyl and methylene blue intraoperatively may have precipitated his clinical deterioration. Indeed, increased muscular tension was temporally related to administration of methylene blue.

Although facial nerve TOF monitoring was used throughout this case, the patient no longer showed response to facial nerve TOF after methylene blue administration, yet he had 4 twitches with fade at the ulnar nerve at the end of the case. The facial nerve has been documented to have myoclonus during SS and may potentially interfere with proper TOF response4[9]. In cases wheb SS may be included in a differential diagnosis, facial nerve myoclonus may offer earlier evidence of a definitive SS diagnosis.

Methylene blue was required in our case to assess for ureteral patency, but it is also frequently used in a diagnostic capacity to assess for the location of ureteral orifices, lymph nodes, lymph vessels, and tumors [10]. Furthermore, it has been used in the treatment of methemoglobinemia, cyanide poisoning, and refractory vasoplegia in cardiothoracic surgery [11,12]. Patients undergoing cardiothoracic surgery are especially at risk of developing serotonin syndrome because of the high incidence of post-cardiopulmonary bypass vasoplegia requiring the use of methylene blue [13–16]. Given the concern for this complication, the FDA published a Drug Safety Communication in 2011, which cautioned about the risk of central nervous system reactions in patients taking serotonergic psychiatric medications who are exposed to methylene blue [2,7,12,17–19]. The FDA recommends that patients who may be exposed to methylene blue should stop taking serotonergic psychiatric drugs from 2 to 5 weeks before any potential exposure, depending on the half-life of the respective drug [12]. However, despite the dangers of methylene blue, the nationwide shortage of alternative dyes such as indigo carmine have made the use of methylene blue more prevalent in clinical practice [20].

Conclusions

It is of vital importance for the anesthesiologist to obtain an accurate medication history in patients taking serotonergic medications and scheduled for procedures requiring the use of methylene blue as an intraoperative urologic marker dye. Patients at risk for serotonergic toxicity should be questioned about central nervous system and neuromuscular symptoms preoperatively and should not be exposed to medications that may precipitate the syndrome. Regional anesthesia should be considered to minimize the perioperative use of opioids which may precipitate serotonin syndrome. Vigilance is of utmost importance to prevent iatrogenic morbidity and mortality associated with the use of drugs known to exacerbate serotonin toxicity.

Statements

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Consent statement: Written consent for this case report was obtained from the patient and his spouse.

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