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Case Report

Serotonin syndrome following left ventricular assist device implantation: A report and institution-specific strategy for prevention

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ABSTRACT

Serotonin syndrome is a potentially lethal complication of antidepressant therapy. Cardiac surgical patients are at particularly high risk of serotonin syndrome due to the prevalence of depression in patients with advanced cardiac disease, many of whom receive multiple serotonergic agents in the perioperative period. Here, we describe a case of postoperative serotonin syndrome following methylene blue administration for perioperative vasoplegia during left ventricular assist device implantation. We additionally describe an institution-specific strategy to minimize future occurrences of serotonin syndrome in this high-risk population.

<**Learning objective:** Antidepressant medication use is prevalent in advanced heart failure patients. With serotonergic antidepressants, perioperative drug interactions may potentiate serious adverse drug events such as serotonin syndrome. In this report, we describe a case of serotonin syndrome following treatment of perioperative vasoplegia with methylene blue and describe steps our institution has implemented to prevent future occurrences.>

Introduction

Serotonergic antidepressants are generally well-tolerated; however, they carry a potential risk of serotonin syndrome. An increase in serotonin concentrations in the central nervous system, serotonin syndrome usually occurs in the setting of patients knowingly or inadvertently taking multiple medications which increase serum serotonin concentrations leading to toxic levels. Drug-drug interactions may additionally play a role when metabolism of serotonergic agents is impaired, particularly in the setting of use of selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) [1,2]. Serotonin syndrome is diagnosed clinically, usually occurring in a concentration-dependent manner with the classic clinical triad consisting of autonomic, neuromuscular, and mental status changes [1].

Use of antidepressant therapy is particularly common in patients suffering from advanced cardiac disease. A meta-analysis in 2006 revealed that 38% of patients with New York Heart Association (NYHA) class III heart failure symptoms and 42% of those with class IV symptoms suffer from depression [3]. Recent reports have described cases of serotonin syndrome following perioperative vasoplegia in cardiac surgical patients on antidepressant medications [4–6]. Vasoplegia is defined by profound hypotension with normal or increased cardiac output and is a common complication of cardiopulmonary bypass, occurring in an estimated 8–10% of patients [7]. Numerous risk factors have been associated with the development of vasoplegia, including blood transfusion, cardiopulmonary bypass, organ transplantation, trauma, sepsis, and medications such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), amiodarone, intravenous heparin, and aprotinin [8]. Methylene

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blue is one of the agents used to treat this refractory hypotension through its attenuation of nitric-oxide mediated pathways [9].

In addition to its hypertensive effects, methylene blue crosses the blood-brain barrier where it inhibits monoamine oxidase, the enzyme responsible for degrading serotonin precursors in the central nervous system [10]. Due to this effect, serotonin toxicity is possible with concurrent use of methylene blue and serotonergic agents. Here, we describe a case of postoperative serotonin syndrome in a patient on long-term sertraline and treated for vasoplegic syndrome with methylene blue. We additionally describe an interdisciplinary approach that our institution has implemented to mitigate the risk of serotonin syndrome in future cardiac surgical patients.

Case report

A 62-year-old male with ischemic cardiomyopathy (left ventricular ejection fraction of 25%, NYHA class IV symptoms), recurrent ventricular tachycardia refractory to ablation, and depression was transferred from a community hospital for evaluation of advanced heart failure therapies. On presentation, he was in decompensated congestive heart failure with runs of ventricular tachycardia precluding inotropic support. Right heart catheterization demonstrated a cardiac index of 2.0 L/min/m^2. Due to hemodynamically significant recurrent ventricular tachycardia in the setting of type O-positive blood, the decision was made to pursue left ventricular assist device (LVAD) placement to expedite advanced therapy. Ventricular tachycardia was thought to be related to elevated pulmonary capillary wedge pressure that would improve with LVAD placement. His home dose of sertraline (50 mg daily) was continued for depression. Preceding surgery, ACE inhibitor/ARB and beta-blocker were stopped due to low blood pressure and low output state; a complete list of medications for 24 h prior to implantation can be found in Table 1. He underwent surgical implantation of the HeartMate III (Abbott, USA) LVAD on hospital day 12. Anesthesia induction was achieved by etomidate 20 mg, fentanyl 500 mcg, and rocuronium 100 mcg. He received appropriate prophylactic antibiotics with cefazolin. Intraoperatively, the patient was noted to be profoundly vasoplegic requiring repeated boluses of phenylephrine, vasopressin, and subsequently methylene blue (2 mg/kg). He returned to the cardiovascular intensive care unit requiring continuous infusions of norepinephrine 0.08 mcg/kg/min, vasopressin 0.04 units/min, epinephrine 0.08 mcg/kg/min, phenylephrine 1 mcg/kg/min, methylene blue 0.5 mg/kg/h, and dexmedetomidine for sedation to a Richmond Agitation-Sedation Scale score of −1 to −2.

Table 1 Current inpatient medication list during day preceding surgery and subsequent diagnosis of serotonin syndrome. Of note, the patient had been taking amoxicillin three times daily at the time of surgery for asymptomatic pyuria with *Enterococcus* grown in urine cultures. An infectious diseases team was consulted and did not feel that infection was a contributing factor at the time of serotonin syndrome diagnosis as blood and urine cultures were negative.

Medication	Dose	Frequency	Route
Sertraline	50 mg	Daily	PO
Amiodarone	400 mg	Daily	PO
Furosemide	80 mg	Daily	IV
Aspirin	81 mg	Daily	PO
Amoxicillin	500 mg	Three times daily	PO
Atorvastatin	40 mg	Daily	PO
Spironolactone	50 mg	Daily	PO
Docusate sodium	100 mg	Twice daily	PO
Cyanocobalamin	500 mcg	Daily	PO
Magnesium oxide	400 mg	Twice daily	PO
Heparin	5000 U	Three times daily	SubQ
Tirofiban	0.15 mcg/kg/min	Continuous	IV

On postoperative day one, the patient became febrile to 40.2 °C with hyperreflexia and ocular clonus on examination. A mild leukocytosis was present (white blood cell count of 16.4 K/L); however, no infectious etiology was identified after infectious workup including blood cultures, urine cultures, chest X-ray, wound inspection, and consultation with an infectious diseases specialist. Serum metabolic studies were additionally unremarkable. Based on his clinical symptoms, a psychiatrist was consulted, who agreed with the primary team's diagnosis of serotonin syndrome secondary to the combination of sertraline, methylene blue, and fentanyl administration. This diagnosis was made by using Hunter Serotonin Toxicity Criteria and took into account the recent use of a known serotonergic agent along with clinical symptoms of ocular clonus and hyperreflexia; hyperthermia further supported this diagnosis [1]. A review of all inpatient medications at the time of diagnosis was conducted. The Naranjo scoring system, which takes into account previously described cases of the adverse drug event, the temporal relationship between drug administration and symptoms, and the presence of alternative causes, indicated a probable direct adverse drug reaction secondary to methylene blue with a score of 6. Serotonergic agents were discontinued. Acetaminophen was started for fever and a continuous infusion of midazolam was initiated at 1 mg/h, resulting in gradual improvement in pyrexia and symptoms over the following days.

Discussion

Serotonin syndrome is a potentially lethal consequence of serotonergic antidepressant therapy that is characterized by altered mental status, neuromuscular changes, and autonomic instability. The diagnosis of serotonin syndrome is made clinically by the use of the Hunter criteria, which involves presence of a serotonergic agent and one of the following symptoms: spontaneous clonus, ocular clonus, agitation, diaphoresis, and tremor, with any form of clonus being the most reliable sign [1]. An improvement from the previous Sternbach's criteria, the Hunter criteria carry 84% sensitivity and 97% specificity for diagnosis of serotonin syndrome when compared to the gold standard of clinical toxicology [1]. Treatment is generally supportive, with the mainstay being prompt cessation of serotonergic agents and benzodiazepines used primarily for symptomatic control; cooling, paralysis, and intubation may be required for severe cases [2].

Although it is unclear whether perioperative serotonin syndrome increased mortality in cardiac surgical patients, advanced heart failure patients generally represent a sicker cohort of surgical patients and are likely to have worse outcomes following perioperative complications such as serotonin syndrome. At our institution, we have introduced measures to limit serotonin toxicity as a future perioperative complication in these patients. All patients on antidepressant medications with serotonergic properties now receive psychiatric evaluation as well as consultation with a clinical pharmacist prior to surgical procedures. When feasible, attempts are made to wean patients from antidepressant medications entirely or to transition to antidepressants with less risk of serotonin syndrome such as bupropion, which has no serotonergic activity. Further attempts are made to avoid the use of additional serotonergic agents in the perioperative period when clinically reasonable. Tramadol, ondansetron, and muscle relaxants, for instance, all have serotonergic activity and are commonly used in hospitalized patients. Given its recent description in post-operative cardiac patients and potential for lethal consequences, it is important for clinicians to promptly recognize serotonin syndrome in susceptible patient populations, particularly those at high risk for vasoplegia such as patients undergoing organ transplantation, requiring cardiopulmonary

bypass, or taking medications linked to vasoplegia. We believe that by implementing a pre-operative evaluation and strategy to limit serotonergic medications, we will decrease the incidence of serotonin syndrome in these patients. To our knowledge, this is the first description of a strategy to mitigate the risk of serotonin syndrome in the perioperative setting.

Conflict of interest

The authors declare that there is no conflict of interest.

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