Case Report

Perioperative adolescent serotonin syndrome secondary to methadone and fentanyl administration: A case report

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Abstract

Serotonin Syndrome (SS) is a serious toxidrome associated with significant morbidity when undiagnosed or improperly managed. We report a perioperative case of serotonin syndrome in an adolescent male on fluoxetine (selective serotonin reuptake inhibitor-SSRI) therapy secondary to an intraoperative combined opioid analgesic regiment. He received low dose methadone and fentanyl for induction for a LeFort osteotomy, the presumed trigger for his perioperative SS. This study demonstrates the essential need for anesthesiologists' vigilance regarding identifying SS, risk factors of SS and implementation of immediate and effective management.

Abbreviations: GAD: Generalized Anxiety Disorder; GPCR: G-protein Coupled Receptor; IV: Intravenous; MAOI: Monoamine Oxidase Inhibitor; MDD: Major Depressive Disorder; OR: Operating Room; PACU: Post-Anesthesia Care Unit; RAE: Right Angle Endotracheal; SERT: Serotonin Transporter; SNRI: Serotonin-Norepinephrine Reuptake Inhibitor; SS: Serotonin Syndrome; SSRI: Selective Serotonin Reuptake Inhibitor.

Introduction

Since 2007, there are less than 20 reports of patients that experiences SS secondary to serotonergic drugs [1]. Before 2007, these reports were not described as SS, or serotonin toxicity, but as toxic effects of specific drugs or therapies themselves. Therefore, we have identified the need for identification, diagnosis and treatment of SS. We describe an adolescent that presented with SS in the perioperative period secondary to opioid analgesic management. Importantly, anesthesiologist must be thorough and weight the risk of medication regiments and assess for possible secondary lethal effects such as SS. A number of drugs used during the administration of general anesthesia, including opioids such as fentanyl and antiemetics such as ondansetron, carry the potential for serotonin toxicity, especially in those patients already taking a prescribed serotonergic medication. Serotonin Reuptake Inhibitor (SSRI) is the most common drug in the treatment of depression and anxiety in adolescents. Therefore, it is essential for anesthesiologists to recognize pa-

tients who may be at risk and the presentation of SS in the perioperative period. We obtained written HIPAA authorization from the patient for this case report.

Case description

An 18-year-old male presented to the operating room for LeFort osteotomy, reconstruction of the mandibular rami, and surgical removal of erupted teeth. He was initially referred for the procedure due to difficult chewing and biting with no improvement during orthodontic therapy. His past medical history was significant for anxiety which was well managed with fluoxetine. He had no known allergies to medication and denied illicit substance use. He reported that he had never received any anesthetic drugs. His physical exam and routine laboratory studies were within normal limits. The patient received 2mg of intravenous (IV) midazolam preoperatively before arrival to the operating room.

The patient was pre-oxygenated and was induced with propofol (200 mg), fentanyl (250 mg), 1% lidocaine (50 mg), and rocuronium (50 mg) IV. Mask ventilation was without issue and he was intubated via video-assisted laryngoscopy using a 7.0 nasal RAE tube. Cefazolin and metronidazole were given as pre-incisional prophylactic antibiotics. Anesthesia was maintained with sevoflurane in oxygen/air (fraction of inspired oxygen 40%) and rocuronium (130 mg in divided doses to maintain 1/4 TOF) to maintain neuromuscular relaxation. The patient had persistent tachycardia, with stable blood pressures, after a total of 6 mg of hydromorphone in divided doses were given after surgical incision. Low dose methadone (total of 10 mg) was given in divided doses which resolved the persistent tachycardia. Intraoperatively, mechanical ventilation maintained an end-tidal carbon dioxide level of 35-40 mmHg. The patient's blood pressure remained unremarkable throughout the procedure. However, the patient's temperature increased slowly from 36.7°C at induction to 37.8°C approximately 4 hours later.

Prior to the end of surgery, the patient received zofran (4 mg), acetaminophen (1 gm), Toradol (30 mg), and dexamethasone (10 mg) IV. Throughout the case a total of 2.1 L of plasmalyte fluid was administered, an estimated 600 mL of blood loss and 550 mL of urine output. The patient received 200 mg of sugammadex for 2/4 TOF for reversal of neuromuscular blockade. After reversal, the patient had delayed arousal and altered mental status from baseline after the return of spontaneous ventilation. There was no evidence of overnarcotization, as patient returned to spontaneous ventilation with rate of 12-14 breaths per minute and pupils were 2-3 mm and reactive. The patient was extubated uneventfully in the OR and taken to the Post Anesthesia Care Unit (PACU) where he was arousable to verbal stimuli and followed commands but not baseline. PACU vital signs were significant for a HR of 115, BP 179/89, temperature of 37.8°C, and an SpO_2 of 96%. He was noted to be diaphoretic on the face and had ice packs placed. He had no signs of muscle rigidity, tremor, clonus, or agitation in PACU.

Post-operative day (POD) 1, the patient's mental status neared baseline but he was noted to have a new onset of intermittent bilateral lower extremity tremors with no etiology or trigger. He endorsed fever and diaphoresis but denied extremity weakness, facial asymmetry, bowel/bladder incontinence, and syncope. Neurology consulted noted increased lower extremity tone, sustained induced clonus on the ankles bilaterally, diaphoresis, tachycardia, and broad hyperreflexia on physical exam. Given these clinical findings and that he: 1) met multiple Hunter Criteria for SS, 2) received serotonergic medications intraoperatively (methadone, fentanyl and zofran), and 3) took scheduled fluoxetine, it was likely he had SS. Subsequently, fluoxetine was held and supportive therapy was continued with close monitoring of potentially worsening or escalating symptoms. He was started on continuous IVF and low dose lorazepam. On POD 3, clonus persisted but tremors were infrequent with resolution of tachycardia and diaphoresis. He was instructed to complete a two-week washout of fluoxetine and discharged to home. On POD 6, his neurological symptoms had completely resolved.

Discussion

SSRIs increase serotonin levels in the synaptic cleft through inhibition of the Serotonin Transporter (SERT) in the presynaptic membrane. This enhances signaling through serotonin receptors, centrally and peripherally, for an extended period of time. While commonly prescribed for the treatment of Major Depressive Disorder (MDD), SSRIs are also used to treat other psychiatric conditions, such as Generalized Anxiety Disorder (GAD). Although safe, efficacious, and generally well tolerated, these drugs are associated with adverse effects such as sexual dysfunction, QT interval prolongation, and serotonin toxicity. SSRIs have also been shown to increase suicidality as well as the risk of developing type II diabetes among children and adolescents. In 2012, approximately 6.2% of adolescents, aged 15-19, were taking an anti-depressant, with 72% specifically on an SSRI [2]. Additionally, antidepressant use among Medicaid-insured adolescents grew 14-fold between 1987 and 2014 and continues to increase [3].

SS is a rare and potentially fatal complication of SSRI use that is defined as a state of serotonin toxicity due to excessive serotonergic activity. Excessive activity can occur through inhibition of serotonin reuptake or breakdown, increased activation of serotonin receptors, and increased serotonin synthesis or release [1,4]. SS is most often seen in patients who are administered more than one serotonergic drug, but it has been reported after a single serotonergic agent or a dosage increase [5]. Manifestations are broad and range from mild to severe, with misdiagnosis common [4]. A diagnosis is made using the Hunter Serotonin Toxicity Criteria requiring one of the following: Spontaneous clonus, inducible clonus with agitation or diaphoresis, ocular clonus with agitation or diaphoresis, tremor with hyperreflexia, or hypertonia with a temperature above 100.4°F and ocular or inducible clonus [6]. Given the importance of an accurate diagnosis, a differential should also include neuroleptic malignant syndrome and malignant hyperthermia, especially in patients receiving anesthetic agents for the first time.

The patient presented here met three of the five Hunter Serotonin Toxicity Criteria after receiving methadone, fentanyl, and hydromorphone intraoperatively after a morning dose of fluoxetine. Methadone is the most problematic of the three drugs administered intraoperatively. It has been previously demonstrated that methadone is a potent inhibitor of SERT and exhibits a strong affinity for the $5\text{-}HT_{2A}$ receptor, a cell surface G-protein coupled receptor (GPCR) for serotonin that has been shown to mediate tremors among rats with SS [1,7,10]. Fentanyl's effects on serotonin signaling pathways differ slightly from methadone and are not as potent [12]. Specifically, fentanyl is a weak inhibitor of SERT but exhibits affinity for both $5\text{-}HT_{1A}$ and $5\text{-}HT_{2A}$ receptors at low concentrations [7,12,13]. A 2015 study conducted in rats provided proof-of-concept that an analgesic dose of fentanyl enhances serotonin toxicity, potentially independent of opioid receptor interactions [14]. The third opioid administered in this case, hydromorphone, has no effect on SERT but is thought to interact with serotonin receptors ($5\text{-}HT_{3A}$) to a less significant degree than methadone and fentanyl [15]. As such, it is likely the least contributory serotonergic agent with regards to our patient's presentation.

First-line treatment of SS includes immediate withdrawal of causative agents and supportive measures such as IV fluids [4]. Patient agitation and tremors can be treated with benzodiazepines as needed. If patients remain hyperthermic with worsening muscle rigidity, intubation and neuromuscular paralysis are

recommended. Cyproheptadine, a 5-HT$_{2A}$ antagonist, is used as an antidote in moderate to severe cases of SS, although little evidence exists to support its role. An initial dose of 12mg is given orally, followed by 2 mg every two hours until symptom improvement is observed. Patients can then be transitioned to maintenance dosing. Of additional note, antipsychotics such as olanzapine have 5-HT$_{2A}$ antagonist properties but should be used with caution due to severe side effect profiles. In the case presented here, fluoxetine was immediately discontinued in favor of a two-week washout. He was also initiated on IV fluids, cooling packs, and lorazepam for agitation. If his symptoms had worsened, neurology planned to initiate treatment with cyproheptadine and upgrade his level of care from general medicine.

Given the increasing prevalence of SSRI use among otherwise healthy adolescents, it is essential for anesthesiologists to recognize the potential for SS in the perioperative setting and tailor medications appropriately. This includes a one-time single or combination dose of any serotonergic drugs. SS is potentially fatal, and practitioner knowledge of presenting symptoms, as well as causative agents, can aid in fast diagnosis and effective, early treatment.

Author Contributions

Emily Anne Smith Bergbower MD PhD: This author participated in intraoperative anesthetic management for this patient, performed a systematic literature review, drafted the case report.

Enoch Cheung, MD: This author participated in intraoperative anesthetic management for this patient, assisted in literature review and edited the case report.

Caron M. Hong, MD, MSc: This author is the senior author and participated in the oversight of anesthetic management for this patient, assessed literature review and edited the case report.

The patient has provided written consent to publish this case report.

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