Serotonin Syndrome in the Perioperative Period

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Herein, we report a patient treated preoperatively with multiple psychiatric medications who developed serotonin syndrome (SS) during the perioperative period. SS was diagnosed using the Hunter Criteria (use of multiple serotonergic drugs preoperatively, hypertonia, and spontaneous clonus) and was presumed to have been triggered by the combination of perioperative and intraoperative serotonergic medications. It is essential that perioperative physicians, especially anesthesiologists, understand the risk factors, clinical scenario, and treatment of SS.
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Serotonin syndrome (SS) is a complication associated with certain psychiatric as well as other serotonergic medications. Although it is a well-known hazard in patients who may overdose these medications, SS may be overlooked during the perioperative period. Although SS is rare, it is essential that physicians caring for patients taking serotonergic medications understand the altered physiology, signs, and symptoms of SS to efficiently diagnose and treat the condition.

CASE DESCRIPTION

A 44-yr-old woman presented to the operating room for hysterectomy, bilateral salpingo-oophorectomy, endometriosis fulguration, and lysis of adhesions (written consent was obtained from the patient to allow us to write this case report). Her medical history included major depression and polysubstance abuse. Two years earlier, the patient experienced a near-lethal overdose that resulted in cardiopulmonary arrest, requiring tracheal intubation, and coma. She recovered fully and was psychiatrically stable for 11 mo on a regimen of benzodiazepine (clonazepam), selective serotonin reuptake inhibitor (SSRI) (duloxetine), anticonvulsants (lamotrigine and topiramate), serotonin secretagogue (lithium), and serotonin receptor blocker (quetiapine). She reported having taken all of her prescribed medications on the day of surgery. The patient denied using illicit drugs and alcohol for the past year. Her physical examination and routine laboratory studies were within normal limits. The patient received midazolam 5 mg IV before arrival to the operating room.

Anesthesia was induced with IV fentanyl 100 μg, propofol 120 mg, and rocuronium 50 mg. Despite difficult mask ventilation, which improved with muscle relaxant administration, the patient's trachea was easily intubated using direct laryngoscopy. Anesthesia was maintained with desflurane in oxygen/air (fraction of inspired oxygen 50%) and 1 IV rocuronium 20-mg bolus. The patient received IV fentanyl 250 μg early in the case followed by IV hydromorphone 2 mg during the remaining 3 operative hours. Intraoperatively, mechanical ventilation maintained an end-tidal carbon dioxide of 32–35 mm Hg. The patient's hemodynamic profile remained stable throughout the 4-h operation. The patient received IV ondansetron 4 mg for nausea/vomiting prophylaxis 1 h before the end of surgery. Lactated Ringer's solution 2.9 L and Hextend (Hospira, Inc., Lake Forest, IL) 0.5 L were administered IV. Estimated blood loss was 350 mL, and urine output was 200 mL. The esophageal temperature at the conclusion of the case was 36.7°C.

At the end of surgery, the patient had 4/4 twitches on train-of-four monitoring. Neuromuscular blockade was reversed with IV neostigmine 5 mg and glycopyrrolate 0.7 mg, and the patient resumed spontaneous ventilation with tidal volumes of 300–400 mL during skin closure. Before emerging from anesthesia, the patient's upper and lower extremities were noted to be rigid with extremely limited passive range of motion. In addition, pupil examination demonstrated horizontal nystagmus. Despite elimination of desflurane to end-tidal concentrations <0.5% and no evidence of overnarcotization, she was unresponsive to verbal and tactile stimulation. Her vital signs were normal (arterial blood pressure 125/58 mm Hg, pulse 98/min, Spo_2 100%, respiratory rate 20 breaths/min). The patient remained tracheally intubated for transfer to the postanesthesia care unit (PACU). In the PACU, the patient had spontaneous, bilateral upper extremity clonus. Her PACU admission temperature was 37.7°C, and arterial blood pressure and heart rate were similar to perioperative values. During the first 45 min in the PACU, the muscle rigidity slowly abated and the patient began following commands. Her trachea was extubated uneventfully. Pain was controlled with hydromorphone IV patient-controlled analgesia on postoperative days (PODs) 0 and 1, followed by oral acetaminophen-hydrocodone on POD 2. The remainder of her postoperative course was uneventful. The patient was discharged home on POD 2. On follow-up, the patient reported "difficulty finding words and concentrating" for 3–4 days after discharge, which ultimately resolved without intervention. She denied extremity weakness, facial asymmetry, and syncope.

DISCUSSION

According to the National Health Statistics Report, physician office visits for treatment of depression increased 27% from 1996 to 2006, making it the third highest increase behind diabetes (40%) and hypertension (28%). Additionally, antidepressants were the

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Table 1. Adaptation of Hunter Serotonin Toxicity Criteria[3]

Use of serotonergic medication, plus one or more of the following
Clonus
Spontaneous[a]
Inducible
Ocular
Agitation
Autonomic dysfunction (i.e., hyperthermia)
Tremor
Hyperreflexia

[a] Serotonin syndrome diagnosed by the combination of serotonergic medication administration and spontaneous clonus. Otherwise, Hunter Criteria require a combination of serotonergic medication and physical examination findings from 2 categories. The Hunter Serotonin Toxicity Criteria: Decision Rules can be found elsewhere.[3]

third most common medication category prescribed in 2006, with SSRIs being the most common in that group.[1] Although SSRIs are effective antidepressant medications for many patients, 1 risk of treatment is serotonin toxicity. SS is described as a triad of altered state of consciousness, autonomic dysfunction (hypertension, tachycardia, and hyperthermia), and neuromuscular excitability. Although clinical manifestations may be relatively mild, life-threatening conditions such as rhabdomyolysis, acute renal failure, and diffuse intravascular coagulation are possible.[2] Diagnostic aids, such as the Hunter Criteria (Table 1),[3] have been used to increase the sensitivity of the diagnosis. No single serotonin receptor has been determined responsible for the phenomenon, but several reviews have implicated serotonin receptor subtype 5-hydroxytryptamine $(HT)_{2A}$ and possibly 5-HT_{1A}.[4–6]

A diagnosis of SS in the perioperative period can be challenging. Although careful attention is given to how medications administered by the anesthesiologist can affect induction, maintenance, and emergence from anesthesia, perioperative physicians must also consider the interaction of outpatient prescriptions with anesthetic and other medications administered. Furthermore, anesthesiologists are often asked to facilitate surgical progress by administering IV dye. Methylene blue (MB), a common choice, is presumed to be an inert dye with little medical consequence. However, Ng and Cameron described 8 cases of SS after MB administration in parathyroidectomy patients taking SSRIs. MB is a phenothiazine derivative with a structure similar to antipsychotic medications and may be a reversible inhibitor of monoamine oxidase A, the enzyme responsible for breakdown of serotonin. In the presence of serotonergic medications such as SSRIs, inhibition of monoamine oxidase A may lead to a serotonin surge and resultant serotonin toxicity.[7,8]

Appropriate treatment for SS involves supportive measures such as stopping the offending agent(s) and providing symptomatic support in the form of IV fluids, hypotensive/hypertensive therapy with direct-acting drugs, and cooling, as indicated. In severe presentations, hyperthermia may be treated with neuromuscular blocking drugs to minimize excessive muscle activity (clonus). Cyproheptadine (a 5-HT_{2a} antagonist) has been used in SS therapy, providing supportive evidence that this receptor is largely responsible for SS. In rare instances, patients may need to be treated for respiratory failure, renal failure, and/or coagulopathy. SS usually resolves within 24 h of discontinuing the offending agent(s).[2,4,6,9]

Table 2. Drugs Implicated in Serotonin Toxicity in the Perioperative Period[2a,b]

Mechanism of action	Drug class and example(s)
Serotonin precursor	L -Tryptophan
Inhibition of serotonin metabolism	Monoamine oxidase inhibitors (isocarboxazid, phenelzine, selegiline, tranylcypromine, linezolid, St. Johns Wort)
Increase in serotonin release	Amphetamines (crystal meth, dextroamphetamine) Lithium MDMA (ecstasy) Cocaine Ethanol
Inhibition of serotonin reuptake	Local anesthetic (cocaine) Phenylpiperidine opioids (fentanyl, dextromethorphan, meperidine, sufentanil, alfentanil, remifentanil) MDMA (ecstasy) SSRIs (fluoxetine, sertraline, trazodone) Tricyclic antidepressants (amitriptyline, nortriptyline, imipramine) Mixed SSRI and NE reuptake inhibitor (duloxetine, venlafaxine)
Serotonin receptor agonism	Buspirone Lithium Sumatriptan Olanzapine LSD

SSRI = selective serotonin reuptake inhibitor; MDMA = 3,4-Methylenedioxymethamphetamine; NE = norepinephrine; LSD = lysergic acid diethylamide.

[a] Sorenson, Susan Pharm D. Utox Update 2002; 4(4). Available at: http://uuhsc.utah.edu/poison/healthpros/utox/Vol4_No4.pdf. Accessed March 6, 2009.

[b] Clinical Pharmacology. Available at: http://clinicalpharmacology-ip.com/default.aspx. Accessed March 6, 2009.

In our patient, we witnessed serotonin toxicity. The physical examination findings in this patient fulfill the Hunter Criteria for diagnosis of SS: use of multiple serotonergic drugs preoperatively, hypertonia, and spontaneous clonus.[3] The concomitant use of duloxetine (which inhibits reuptake of serotonin and norepinephrine), lithium (which increases serotonin synthesis and release), and quetiapine (which antagonizes serotonin receptor subtype 5-HT_2) likely increased her risk of serotonin toxicity in the perioperative period (Table 2).[2]

In addition to perioperative medications, drugs given during surgery may have ultimately been responsible for the serotonin toxicity. Administration of fentanyl (a phenylpiperidine opioid) early in the case may have predisposed her to serotonin toxicity. Ailawadhi et al.[10] described a patient treated preoperatively with citalopram who developed SS 24 h after receiving a fentanyl patch for pain control. This patient's symptoms of SS abated within 24 h of fentanyl

patch removal and did not recur with oxycodone (a phenanthrene opioid). Alkhatib et al.[11] described another case of SS involving a patient treated preoperatively with sertraline who received fentanyl for sedation during esophagogastroduodenoscopy. This patient received no other serotonergic medications. Finally, a case report by Szakaly and Strauss[12] implicated the combination of perioperative bupropion plus intraoperative dextromethorphan (a phenylpiperidine opioid) in precipitation of a severe form of SS in a patient undergoing oral and maxillofacial surgery. Although opioids in the phenylpiperidine class have been linked to SS, other opioids have not. It seems prudent to avoid administering phenylpiperidine opioids to patients who may be at risk for SS perioperatively.

Ondansetron was administered to our patient during surgery for nausea prophylaxis. Turkel et al.[13] described a patient who developed SS after receiving a combination of mirtazapine and ondansetron. It is postulated that ondansetron may increase systemic serotonin levels via its blockade of 5-HT_3 receptors, leading to stimulation of other serotonin receptor subtypes (including 5-HT_{1a} and 5-HT_{2a}). Because of this potential interaction, one should consider omitting ondansetron from the perioperative medication regimen in patients taking serotonergic medications.

Time and close observation were effective treatment for our patient. Although fentanyl may have contributed to the patient's muscle rigidity and other serotonergic findings, allowing time for metabolism and elimination of the drug obviated the need to administer systemic therapies for SS. In addition, the patient received appropriate IV hydration during surgery.

The differential diagnosis for this presentation includes neuroleptic malignant syndrome, malignant hyperthermia, opioid-induced muscle rigidity, and seizure. Neuroleptic malignant syndrome and malignant hyperthermia would have been associated with more dramatic hyperthermia and cardiopulmonary consequences; spontaneous resolution would have been less likely. Opioid-induced muscle rigidity is a consideration, but the lack of large boluses of opioids and the stable respiratory variables make this diagnosis doubtful. Although seizure is a possibility, particularly given the patient's difficulty concentrating on POD 3, the patient did not have a seizure history and was taking 2 anticonvulsant medications. Her difficulty with concentration and word finding seem not to be temporally related to the SS episode but could have been a result of cognitive dysfunction after general anesthesia, postoperative pain control, or postoperative sleep disruption.

In an age of increasing prescription of psychiatric medications, it is essential that practitioners involved in the care of patients using serotonergic medications realize the possibility of SS presenting in the perioperative setting. Because SS is strictly a clinical diagnosis and has potentially life-threatening consequences, knowledge of the signs and symptoms, and drugs that may precipitate the condition, will aid in early diagnosis and effective treatment of the condition.

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