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Intraoperative care to avoid precipitation of serotonin syndrome in an at-risk adolescent presenting for posterior spinal fusion

A. Elhamrawy[1], J. D. Tobias[1,2]

[1]Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital, Columbus, Ohio, USA
[2]Department of Anesthesiology & Pain Medicine, The Ohio State University College of Medicine, Columbus, Ohio, USA

Corresponding author: J. D. Tobias, Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital, Columbus, Ohio, USA. Email: Joseph.Tobias@Nationwidechildrens.org

Keypoints

1. Serotonergic excess and the development of serotonin syndrome can be precipitated by blockade of its extracellular clearance or increased release from serotonergic neurons. This generally results from a combination of prescription and over-the-counter medications.
2. Initial signs and symptoms include autonomic dysfunction with tachycardia, shivering, diaphoresis, inducible clonus, and agitation. Serotonin syndrome may progress to life-threatening complications including hemodynamic instability, hyperthermia, sustained clonus, muscle rigidity, and rhabdomyolysis.
3. During anesthetic care, an accurate diagnosis may be difficult as the signs and symptoms may be attributed to other causes or masked by general anesthesia. The differential diagnosis may include other life-threatening conditions including neuroleptic malignant syndrome, status epilepticus, malignant hyperthermia, and anticholinergic toxicity.
4. Preoperative medications with serotonergic activity should be held for 5-7 days prior to anesthetic care. However, patients may need to continue these medications to avoid exacerbation of mental health issues. Intraoperatively, other medications that augment serotonergic activity should be limited including specific opioids (fentanyl, meperidine, oxycodone, and tramadol), anti-emetic agents (ondansetron and granisetron), as well as other miscellaneous agents (methylene blue, hydralazine, and linezolid).

Abstract

Serotonin syndrome is an uncommon adverse reaction associated with specific psychotropic and serotonin enhancing medications. It can be precipitated by blockade of the extracellular clearance of serotonin or its increased release from serotonergic neurons. Clinical features include autonomic signs, neuromuscular changes, and altered mental status with life-threating complications including hemodynamic instability, hyperthermia, muscle rigidity, and rhabdomyolysis. Given the multiple medications used during the perioperative period, there are numerous anecdotal reports of serotonin syndrome presenting during perioperative care. We present an adolescent who required anesthetic care during posterior spinal fusion. She was at risk for serotonin syndrome due to the potential interaction of prescription, over-the-counter, and anesthetic medications. The etiology, presentation, and treatment of serotonin syndrome are presented. Previous reports of serotonin syndrome during anesthetic care are reviewed and interventions to prevent its perioperative occurrence presented.

Keywords

serotonin syndrome; serotonin

Introduction

Serotonin syndrome is an uncommon adverse reaction associated with certain psychotropic and serotonin-enhancing medications.[1,2] Serotonin syndrome may also be precipitated by the combination of prescription medications, over-the-counter adjuncts, and commonly used intravenous anesthetic medications (opioids). Serotonergic excess can be precipitated by blockade of its extracellular clearance or increased release from serotonergic neurons (Figure 1).

Case reports of adverse physiologic effects related to serotonin excess following the administration of psychotropic medications were first published in the 1950s while the term "serotonin syndrome" first appeared in the 1980s.[3,4]

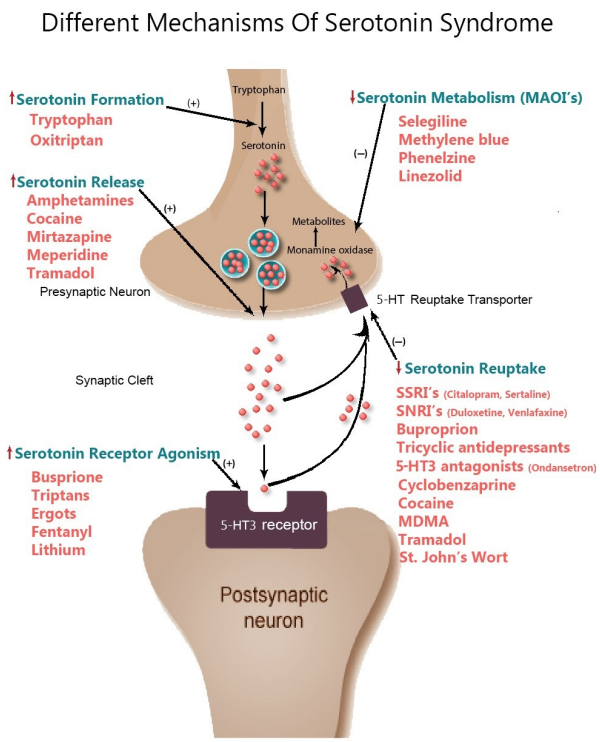

Figure 1. Serotonin syndrome may also be precipitated by any combination of prescription medications, over-the-counter adjuncts, and commonly used intravenous anesthetic medications including opioids. Serotonergic excess can be precipitated by increased formation, increased release, decreased metabolism, blockade of its extracellular clearance (decreased reuptake), or increased agonism at the receptors. 5-HT = 5-hydroxytryptophan; MDMA = 3,4-Methylenedioxymethamphetamine, commonly known as ecstasy; MAOI = monoamine oxidase inhibitor.

Serotonin toxicity has a wide spectrum of clinical features including autonomic signs, neuromuscular changes, and altered mental status.[3] Common initial signs and symptoms include tachycardia, shivering, diaphoresis, inducible clonus, and agitation. These may progress to life-threatening complications including hemodynamic instability, hyperthermia, sustained clonus, muscle rigidity, and rhabdomyolysis. Although it is a well-known hazard in patients who overdose on psychotropic medications, the signs and symptoms may be missed during the perioperative period or attributed to other intraoperative emergencies including malignant hyperthermia.[4,5] We present an adolescent who required anesthetic care for posterior spinal fusion and was at risk for postoperative serotonin syndrome due to chronic use of multiple medications. The etiology, presentation, and treatment of serotonin syndrome is presented. Previous reports of serotonin syndrome during anesthetic care are reviewed and interventions to prevent its perioperative occurrence presented.

Case report

Review of this case and presentation in this format followed the guidelines of the Institutional Review Board approval at Nationwide Children's Hospital (Columbus, Ohio). A 15-year-old adolescent with a history of anxiety and attention deficit disorder presented for posterior spinal fusion to treat idiopathic scoliosis. Her surgical history was remarkable for adenoidectomy and tympanostomy tube placement 4-5 years ago. There was a strong family history of psychiatric disorders including anxiety in her maternal grandmother, natural father, and natural mother, bipolar disorder in her great uncle, and depression in her natural father and mother. Current home medications included dexmethylphenidate extended release (30 mg by mouth every morning), risperidone (0.5 mg by mouth every morning), melatonin (5 mg by mouth at bedtime), St. John's Wort (300 mg by mouth twice daily), cetirizine (10 mg once daily), and sertraline (25 mg by

mouth at bedtime). There were no medication allergies. As her pre-admission testing phone interview was conducted only 48 hours prior to surgery, it was not possible to hold the St. John's Wart for 5 days prior to surgery per our usual routine. Given these concerns, a consultation was obtained from our pharmacy services (see below) and it was decided to proceed with the scheduled surgery. Preoperative physical examination revealed an adolescent in no acute distress. She had idiopathic scoliosis with a dextro-scoliotic curve from T5-T11 measuring 50º and a levo-scoliotic curve from T11-L4 measuring 63º. Airway examination revealed a Mallamapti class I view with a thyromental distance greater than 3 fingerbreadths. Cardiac and lung examination were within normal limits. Preoperative laboratory evaluation including a complete blood count, coagulation profile, and urine analysis were normal. The hemoglobin was 13.3 gm/dL with a hematocrit of 40.6%. She was held *nil per os* for 8 hours. She was transported to operating room where routine American Society of Anesthesiologists' monitors were applied. A peripheral intravenous cannula was placed after the inhalation of 50% nitrous oxide in oxygen and midazolam (2 mg) was administered intravenously. Anesthesia was induced with propofol (150 mg), sufentanil (25 µg), and lidocaine (100 mg). Bag-valve-mask ventilation was provided without difficulty and neuromuscular blockade was achieved with rocuronium (25 mg). Her trachea was intubated with a 7.0 mm cuffed endotracheal tube on the first attempt via direct laryngoscopy with a Macintosh 4 laryngoscope. After the induction of anesthesia, a 20-gauge left radial arterial line and a second peripheral intravenous cannula were placed. Tranexamic acid was administered for prevention of fibrinolysis and to limit intraoperative blood loss (50 mg/kg bolus dose followed by an infusion at 5 mg/kg/hour). Baseline neurophysiological monitoring including motor evoked potentials (MEP) and somatosensory evoked potentials (SSEP's) were obtained. The patient was turned and positioned prone. Per our usual practice to allow for neurophysiological monitoring during spinal surgery, maintenance anesthesia included desflurane titrated to maintain the bispectral index (BIS) at 50-60, lidocaine (1 mg/kg/hour), and a sufentanil infusion (0.1-0.4 µg/kg/hour) with a single intraoperative dose of methadone (0.1 mg/kg). Blood avoidance techniques included intraoperative cell saver and clevidpiine (1-5 µg/kg/min) to provide controlled hypotension with a mean arterial pressure of 55-65 mmHg. Cefazolin (2 grams every 3 hours) was administered for prophylaxis against surgical site infections. Intraoperative intravenous fluids included Normosol®-R (2500 mL), 5% albumin (250 mL), and cell saver autologous blood (145 mL). Estimated blood loss was 575 mL. No allogeneic transfusions were required during the 7 hours surgical procedure. Dexamethasone (8 mg) was administered for prophylaxis against perioperative nausea and vomiting. Hydromorphone (total dose of 0.5 mg), dexmedetomidine (20 µg), and acetaminophen (1000 mg) were administered to supplement postoperative pain control. At the completion of the surgical procedure, residual neuromuscular blockade was reversed with sugammadex (100 mg) and her trachea was extubated. The patient was transferred to Post Anesthesia Care Unit for observation of hemodynamic and respiratory function. Postoperative analgesia was provided by patient-controlled analgesia with hydromorphone as well around-the-clock dosing of acetaminophen and ketorolac. On postoperative day 1, the analgesic regimen was transitioned to oral medications. Her postoperative course was unremarkable, and she was discharged home on postoperative day 3 after reviewing all medications with the clinical pharmacist.

Discussion

Serotonin ($C_{10}H_{12}N_2O$) is an important neurotransmitter that plays a key role in the regulation of various physiologic functions including mood, sleep, digestion, nausea, wound healing, bone health, and blood coagulation. Tryptophan, the main precursor of serotonin, undergoes two metabolic processes including a decarboxylation step and a hydroxylation step resulting in the formation of serotonin or 5-hydroxytryptophan (5-HT). Once serotonin

is formed, it is packaged into pre-synaptic vesicles for storage. In response to various stimuli, serotonin is released into the synaptic cleft, binding to post-synaptic receptors, thereby exerting its physiologic effects. The specific physiologic effects are regulated by various types of serotonin receptors including 5-HT_{1A} (temperature and feeding regulation), 5-HT_{2A} (peripheral vasoconstriction platelet aggregation), 5-HT_{2B} (gastric contraction), 5-HT_3 (nausea, vomiting and anxiety), and 5-HT_4 (gastrointestinal motility).[6] To date, a total of 7 serotonin receptors have been identified. 5-HT1 receptors are mediated by adenylate cyclase and are the primary site of action of medications that control migraine headaches such as sumatriptan. These receptors are primarily found in the limbic system. 5-HT2 receptors stimulate the enzyme, phosphoinositide-specific phospholipase, and their antagonism leads to the therapeutic effect of several antipsychotic medications such as risperidone. The 5-HT3 receptor is a ligand-gated cation channel predominantly expressed by neurons. This is the pharmacological site of action for anti-emetic agents such as ondansetron. The activity of the more recently identified receptors including 5-HT5, 5-HT6 and 5-HT7 are being investigated.

Dissipation of the effects of serotonin occurs by reuptake of serotonin into the pre-synaptic terminal via a transporter and its subsequent catabolism by monoamine oxidase. From this pathophysiologic explanation as noted in Figure 1, three general classes of medications have the potential to increase the concentration of serotonin within the synaptic cleft by decreased metabolism (monoamine oxidase inhibitors [MAOIs], decreased reuptake though inhibition by selective serotonin reuptake inhibitors (SSRIs) or increased serotonin formation or release.[7,8] An additional potential mechanism for the development of serotonin syndrome is increased agonism of serotonin at its receptor.

Serotonin syndrome remains an uncommon albeit life-threatening event. There is no confirmatory laboratory test or direct correlation reported between actual serotonin concentrations and disease severity.[4] Severe life-threatening serotonin syndrome most commonly results from a drug-drug interaction, specifically medications with MAO inhibitor activity combined with medications that augment serotonin release or those that block its reuptake such as antidepressant agents. Serotonin syndrome can also result following an acute drug overdose, a routine therapeutic dose increase, or unanticipated drug-drug interactions.[8-11] The latter has been anecdotally reported during the perioperative setting when the patient's chronic medications interact with the combination of intraoperative medications, some of which may be assumed to have limited serotonergic activity (Table 1).[5,12-19]

Bartakke et al. reviewed a total of 31 cases of presumed serotonin syndrome from 29 case reports.[4] They noted a median patient age of 58 years with a slight predominance of female gender (61%). The most common clinical manifestations included agitation, delayed awakening from anaesthesia, and confusion. Neuromuscular manifestations included nystagmus, clonus, and myoclonic jerks. Autonomic involvement was most commonly manifested as hyperthermia, tachycardia, and diaphoresis. The most commonly cited surgical procedures were cardiac followed by orthopedic and general surgical procedures. The authors attributed the high incidence in cardiac surgery to the administration of high doses of synthetic opioids. A majority of patients were chronically taking an SSRI (65%) prior to surgery while the most commonly cited intraoperative inciting medications were methylene blue (52%) and fentanyl. Other identified triggering medications included phenylpiperidine derivatives (meperidine, remifentanil, and dextromethorphan), ondansetron, cyclobenzaprine, oxycodone, and lidocaine. During anesthetic care, various combinations of medications may be used to provide anesthesia, treat pain, and prevent postoperative concerns including nausea and vomiting. In most clinical scenarios, despite the potential

Case report	Age (years)	Procedure	Outpatient Medication	Intraoperative medication
Takata J et al.[5]	31	Laparoscopic ovarian cystectomy.	Duloxetine	Fentanyl, remifentanil
Schumacher LD et al.[12]	60	LVAD implantation under general anesthesia.	Escitalopram, citalopram	Fentanyl, methylene blue
Smischney NJ et al[13]	70	Photo-vaporization of prostatic cancer.	Venlafaxine	Fentanyl and meperidine
Lee C et al.[14]	51	Emergency appendectomy.	None	Fentanyl and palonosetron (intraoperatively); meperidine (postoperatively for shivering)
Guo SL et al.[15]	41	Right clavicular fracture (positive history of previous serotonin syndrome after clomipramine).	History of clomipramine induced serotonin syndrome	Meperidine (postoperatively)
Matchanov O et al.[16]	67	Elective trans-lumbar discectomy and interbody fusion.	Tramadol (as treatment for chronic pain)	Methadone, remifentanil
Rang ST et al.[17]	60	Excision of a chest wall myxofibrosarcoma with reconstruction.	Paroxetine	Fentanyl
Jahr JS et al.[18]	18	Excision of a fractured sesamoid bone of the left foot under regional anesthesia.	Sertraline (Started 2 weeks before surgery)	Fentanyl, midazolam, and lidocaine (postulated displacement of sertraline from protein binding)
Davis JJ et al.[19]	23	Patellar realignment of the right knee (general and regional anesthesia).	Fluoxetine	Remifentanil

Table 1. Reports of perioperative serotonin syndrome. *LVAD = left ventricular assist device*

for many of these medications to augment serotonergic activity, the additive effects do not result in clinical manifestations of serotonin syndrome. However, in the presence of specific comorbid conditions or when administered in association with other chronic medications (prescription, herbal or over-the-counter), there is a potential for exaggerated serotonergic effects. In many of the cases outlined in the table and the report of Bartakke et al, the patient was on a preoperative medication that augments serotonergic activity such as an SSRI, an antidepressant, or an anti-psychotic medication. In such scenarios, preoperative awareness of the role of these agents and the potential for the development of serotonin syndrome is imperative to allow for safe perioperative care with adjustment of intraoperative medications as needed. This was the case in our patient who was on a psychotropic medication as well as an over-the-counter herbal medication that is known to augment serotonergic activity, St John's Wart. The most common initial signs and symptoms include muscle rigidity, tonic-clonic seizures, respiratory failure, coma, delirium, confusion, myoglobinuria, and severe hyperthermia ≥ 40°C.

During anesthetic care, an accurate diagnosis may be difficult as the signs and symptoms may be attributed to other causes or masked by general anesthesia. The differential diagnosis may include other life-threatening conditions including neuroleptic malignant syndrome, status epilepticus, malignant hyperthermia, anticholinergic toxicity, opioid withdrawal, perioperative delirium, and muscle rigidity induced by opioids.[20] Management of serotonin syndrome begins with identification of at-risk patients and adjustment of the intraoperative care to avoid medications with significant serotonergic effects. In our patient, given these concerns, preoperative consultation with the hospital-based Pharmacy Services was obtained. When feasible, preoperative medications with serotonergic activity should be held for 5-7 days as feasible. However, patients may need to continue these medications to avoid exacerbation of mental health issues. Other medications that augment serotonergic activity should be avoided or limited including specific opioids (fentanyl, meperidine, oxycodone, and tramadol), antiemetic agents (ondansetron and granisetron), as well as other miscellaneous agents (methylene blue, hydralazine, and linezolid).[21] Treatment options are outlined in Figure 2 and is instituted based on the severity of the clinical signs and symptoms.

Serotonin syndrome is a life-threating systemic adverse effect related to the end organ effects of increased serotonergic activity. Serotonergic excess can be precipitated by increased formation, increased release, decreased metabolism, blockade of its extracellular clearance (decreased reuptake), or increased agonism at the receptors. Clinical features include autonomic signs, neuromuscular changes, and altered mental status with life-threating

complications including hemodynamic instability, hyperthermia, muscle rigidity, and rhabdomyolysis.

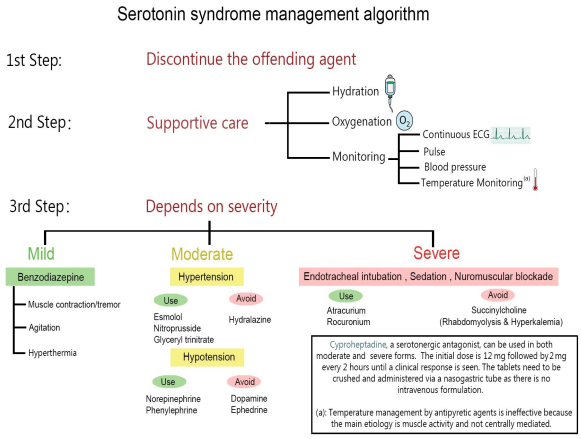

Figure 2. Serotonin syndrome management algorithm divided into three steps based on the severity of the clinical signs.

Given the multiple medications used during intraoperative care, serotonin syndrome can be precipitated especially in patients who are chronically taking psychotropic medications such as SSRIs. Preoperative awareness of such patients may be facilitated by electronic medical record technology to identify at risk patients. In these patients, medications with significant serotonergic activity should be avoided whenever feasible.

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