A case report of suspected serotonin syndrome following administration of fentanyl

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Background: Serotonin syndrome (SS) is a potentially life-threatening drug-induced toxidrome that can occur because of an overdose of a serotoninergic drug or the combination of multiple drugs with serotoninergic activity at therapeutic doses, leading to an increase in serotonergic activity in the central and peripheral nervous system. SS in the setting of general anesthesia is uncommon but possibly underdiagnosed because of the variability in its severity and symptomatology. This report presents a case of severe SS following the administration of fentanyl during induction of general anesthesia. Additionally, it provides a brief overview of the pathophysiology, clinical features, management strategies, and commonly used drugs by anesthesiologists that can potentially result in a fatal interaction.

Case Description: This report describes the case of an elderly male patient who was diagnosed with severe SS during video-assisted thoracoscopic surgery (VATS) on the right side. The patient's home medications included sertraline and aripiprazole. During induction of general anesthesia with the administration of fentanyl, the patient became restless and severely hypertensive. He became unresponsive to verbal commands, developed pinpoint pupils, and had myoclonic jerking of his lower extremities. The patient was intubated for airway protection, treated with nitroglycerin, labetalol, and hydralazine for hypertension and underwent neuroimaging. The patient met the Hunter serotonin toxicity criteria for SS. He was treated in the intensive care unit with supportive care and mechanical ventilation, and his sertraline and aripiprazole were discontinued. The patient eventually recovered and was extubated after his neurologic status returned to normal.

Conclusions: Clinical features of SS include a spectrum of signs and symptoms related to neuromuscular abnormalities, autonomic hyperactivity, and mental state changes which can be masked under general anesthesia. However, if severe SS occurs, it can be life-threatening and early recognition and prompt treatment are vital to saving the patient's life. This case highlights the importance of considering SS in the differential diagnosis and highlights the need for careful medication management in the perioperative setting.

Keywords: Case report; fentanyl; serotonin; surgery

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Introduction

Serotonin syndrome (SS), also referred to as serotonin toxicity, is an iatrogenic drug-induced toxidrome caused by an overdose of a serotoninergic drug or by the combination of two or more drugs with serotoninergic activity at therapeutic doses (1). SS is characterized by a triad of symptoms: neuromuscular hyperactivity, autonomic nervous system hyperactivity, and altered mentation. The symptoms are typically self-limited, but can range from mild to severe, and sometimes even fatal. SS has been described in the literature for decades and is a complication of polypharmacy. During the perioperative period, opioids and other serotonergic drugs are often co-administered, and it is challenging to diagnose SS as it can mimic other conditions such as malignant hyperthermia, thyroid storm, and neuroleptic malignant syndrome (1). The diagnosis of SS is also complicated by the variability in serotonin metabolism, overlapping symptoms, and limitations in diagnostic criteria, especially in the context of general anesthesia. Therefore, it is crucial for anesthesiologists to be aware of the potential for SS to occur during the perioperative period, given the common use of serotonergic agents including opioids. It is essential for an anesthesiologist to diagnose severe SS promptly in the perioperative setting as severe case of SS can be fatal. The treatment for SS depends on the severity of symptoms and involves discontinuing the causative medication and providing supportive care for the manifesting symptoms, which may involve intensive care with hemodynamic monitoring, cooling measures, mechanical ventilation, and administration of benzodiazepines, beta-blockers, neuromuscular blockers, and cyproheptadine.

We report a rare case of severe SS in an elderly male following the administration of fentanyl during induction of general anesthesia. The Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database found only 43 cases of SS involving opioid and serotonergic drug use between 1969–2013. We present this case in accordance with the CARE reporting checklist (available at https://amj.amegroups.com/article/view/10.21037/amj-22-44/rc).

Highlight box

Key findings

- The patient developed severe SS following the administration of fentanyl during induction of general anesthesia.
- The patient was diagnosed with SS based on the presence of specific symptoms and a clear link to medication exposure.

What is known and what is new?

- SS is a drug-induced condition caused by an overdose of a serotoninergic drug or the combination of two or more drugs with serotoninergic activity at therapeutic doses.
- This case report describes a specific instance of severe SS in an elderly male following the administration of fentanyl during induction of general anesthesia.

What is the implication, and what should change now?

- Anesthesiologists should be aware of the risk of SS in patients taking serotoninergic drugs and should be prepared to recognize and treat the condition if it occurs.

Case presentation

An elderly male presented with a small, slowly expanding right upper-lobe solitary pulmonary nodule of 1.8 cm in diameter. He was scheduled for right video-assisted thoracoscopic surgery (VATS) and right upper-lobe wedge resection with possibility of right upper lobectomy on February 5, 2021. The patient had a medical history of hypertension and was taking nifedipine, lisinopril, and propranolol. He also had a history of chronic post-traumatic stress syndrome and depression, for which he was prescribed sertraline and aripiprazole. He was diagnosed with neuroleptic-induced parkinsonism 5 years earlier in 2016, and perphenazine, a first-generation antipsychotic, was replaced with aripiprazole, a second-generation antipsychotic with a lower risk of extrapyramidal side effects.

A preoperative physical exam was unremarkable. The patient had taken nifedipine, propranolol, sertraline, and aripiprazole on the morning of surgery, and lisinopril was withheld as instructed. Peripheral intravenous line and arterial line were placed, and the patient was taken to the operating room where he was given 100 mcg fentanyl intravenously. While preparing for anesthesia induction, the patient became restless and hypertensive. An additional 50 mcg of fentanyl was given along with 50 mg propofol, intravenously. However, the patient remained hypertensive. A focused neurologic exam was then performed, and the patient was confused, nonverbal, not following commands, and his pupils were pinpoint without gaze preference. The patient's airway was supported briefly while waiting for the effect of the propofol to subside by redistribution. Furthermore, nonsynchronous myoclonic twitching and jerking of lower extremities were observed. The

patient's hypertension was treated with repeated boluses of intravenous nitroglycerin 60 mcg, which only had a transient effect on blood pressure (BP). This was followed by 10 mg followed by 20 mg intravenous labetalol, with minimal effect on BP; and 20 mg hydralazine, intravenous. The patient's BP decreased after 5 to 10 minutes. The patient's Glasgow coma scale was less than 8; therefore, he was intubated, after administering propofol and succinylcholine, for airway protection and to facilitate immediate neuroimaging. The patient was given a single dose of midazolam 2 mg, and propofol infusion was started for ongoing sedation along with nicardipine infusion for additional BP control.

The patient was transferred to the intensive care unit after neuroimaging, sedated, and supported on mechanical ventilation; at this time, his BP was back at the baseline. The patient remained unresponsive under sedation; the myoclonic jerks continued, and clonus was inducible in the lower extremities. Magnetic resonance imaging with magnetic resonance angiography showed no signs of cerebral vascular accident, large vessel occlusion, or other acute vascular abnormalities. The patient met the Hunter serotonin toxicity criteria for SS with spontaneous myoclonus and inducible clonus and clear medication exposure: he had been using sertraline and aripiprazole regularly and was given fentanyl shortly before the hypertensive emergency. The patient's sertraline and aripiprazole were withheld, propofol sedation was stopped, and he was extubated the next day, on February 6, 2021. The patient's neurologic status returned to baseline, and he was transferred back to the floor the next day and discharged home on day 4, February 9, 2021. He subsequently underwent VATS successfully in September 2021, without any complications.

All procedures performed in this case report were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). The authors obtained written Health Insurance Portability and Accountability Act (HIPAA) authorization from the patient for the publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Serotonin is a key neurotransmitter in the central and peripheral nervous system, synthesized primarily in the enterochromaffin cells of the gastrointestinal tract (2). There are a variety of receptors for serotonin, including at least five families of 5-hydroxytryptamine 1 (5-HT1) receptors and three families of 5-HT2 receptors, distributed both peripherally and centrally. In the central nervous system, serotonin is primarily found in the brainstem and contributes to cerebral vasodilation. Peripherally it is found in platelets, the gastrointestinal tract, kidneys, and lungs and contributes to vasoconstriction, uterine contraction, bronchoconstriction, and gastrointestinal motility (2-5).

SS was initially observed during concurrent administration of meperidine and iproniazid, an antituberculosis drug that inhibits monoamine oxidase (1,6). Although not fully understood at the time, multiple cases were reported with toxic reactions (1). It was only in 1991 that the first comprehensive clinical review was reported by Sternbach (7,8). The FDA FAERS database identified only 43 cases of SS between 1969 and 2013 in which opioids were used with other serotonergic agents (7,9). The review excluded meperidine, tramadol, and tapentadol, which were already labeled for the risk of SS.

SS is a manifestation of abnormally raised intrasynaptic concentrations of serotonin, which results in the hyperstimulation of both central and peripheral serotonin receptors, primarily 5-HT1A and 5-HT2A receptors (5,6,10). SS can result from an overdose of a single serotoninergic drug or the combination of two or more drugs with serotoninergic activity (*Table 1*). A single dose of a serotoninergic drug can produce serotonin toxicity in patients with renal failure, cirrhosis, or cytochrome P4502D6 deficiency (5,9,10). Increased serotonin levels can be secondary to alterations in serotonin transport, binding, or metabolism (*Table 2*). A 5-HT3 antagonist such as ondansetron can also cause SS by increasing the amount of serotonin available to bind 5-HT1A and 5-HT2A receptors (6). Serotonin transporter (ST) is a transport protein on platelets and presynaptic terminals of neurons and is responsible for removing serotonin from the synaptic cleft to maintain low circulating levels of serotonin (1,11). Opioids such as dextromethorphan, tramadol, and methadone inhibit STs. By contrast, synthetic opioids such as fentanyl and meperidine directly activate receptors (*Figure 1*).

The exact incidence of SS is uncertain and is likely under-recognized or under-reported since the mild cases are self-limiting (6,10,12,13). The clinical features of SS are classically characterized by the triad comprising neuromuscular hyperactivity, autonomic nervous system hyperactivity, and altered mentation (1,8,10). Hypertonia and rigidity classically affect the lower limbs first and then involve the truncal muscles, impairing ventilation (5,6,13).

Table 1 Serotoninergic drugs with potential to cause serotonin syndrome

Drug class	Name
SSRI	Fluoxetine
	Citalopram
	Olanzapine
	Fluvoxamine
	Paroxetine
SNRI	Venlafaxine
	Duloxetine
	Sibutramine
MAOI	Phenelzine
	Selegiline
	Tranylcypromine
Triptan	Sumatriptan
	Rizatriptan
	Almotriptan
	Zolmitriptan
	Eletriptan
	Frovatriptan
	Naratriptan
Opioids	Fentanyl
	Methadone
	Meperidine
	Dextromethorphan
Others	Ondansetron
	Metoclopramide
	Linezolid
	Methylene blue
	Tricyclic antidepressants
	Valproic acid
	Carbamazepine
	Cocaine
	Methamphetamine
	Buspirone
	Trazodone
	Cyclobenzaprine
	Ergot alkaloids
	5-hydroxytryptophan
	Lithium
	l-tryptophan
	Mirtazapine
	St. John's wort

SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; MAOI, monoamine oxidase inhibitor.

Spontaneous, inducible, and ocular clonus has been strongly associated with serotonin toxicity (8). The various drugs administered during general anesthesia will mask or alter the clinical features of SS (1). It is impossible to assess mentation in a patient under general anesthesia or observe neuromuscular hyperactivity in a patient who is paralyzed with neuromuscular blockade (1). Blood levels of serotonin in SS do not correlate with clinical findings, and there are no specific diagnostic tests.

Hunter serotonin toxicity criteria is the most widely applied diagnostic criteria and is found to be more sensitive and specific than the earlier Sternbach's criteria (1,8). SS is diagnosed if in the presence of a serotonergic agent the patient develops any one of the following:

(I) Spontaneous clonus;
(II) Inducible or ocular clonus with agitation or diaphoresis;
(III) Inducible or ocular clonus with hypertonia and hyperthermia;
(IV) Tremor and hyperreflexia.

Differential diagnoses include malignant hyperthermia (muscular rigidity persists with neuromuscular blockade in malignant hyperthermia but subsides in SS), hyperthyroidism and thyroid storm, neuroleptic malignant syndrome, anticholinergic toxidrome syndromes, pheochromocytoma, and carcinoid tumor (1,5,7,8,10). The urgency to manage SS depends on the severity of symptoms. Management is primarily supportive care along with discontinuation of the offending agents (5,6). Moderate to severe cases may require intensive care along with active cooling, hemodynamic monitoring, paralysis, and ventilation. Benzodiazepines are used to treat agitation, catatonic features, muscle

Table 2 Mechanisms to increase intrasynaptic levels of serotonin

Mechanism	Medications
Increase production of 5-HT or its precursor	Buspirone, L-dopa, lithium, LSD, l-tryptophan, trazodone
Increase release of 5-HT into the synaptic cleft	Amphetamines, cocaine, MDMA, fenfluramine, reserpine, meperidine, methadone, dextromethorphan
5-HT receptor agonism	Fentanyl, meperidine, methadone aripiprazole, lithium, metoclopramide, dihydroergotamine, triptan
Decrease reuptake of 5-HT	SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
	Opioids: methadone, meperidine, tramadol
	SNRIs: duloxetine, venlafaxine
	TCAs: amitriptyline, imipramine, nortriptyline, desipramine
Decrease metabolism of 5-HT	MAOIs:
	Irreversible: phenelzine, tranylcypromine, selegiline
	Reversible: linezolid, thiazine dye such as methylene blue

5-HT, 5-hydroxytryptamine; LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; MAOI, monoamine oxidase inhibitor.

spasms, and hyperadrenergic reactions. Beta-blockers blunt adrenergic hyperactivity. Propranolol has 5-HT1A antagonist activity, which makes it particularly well suited. In severe cases, neuromuscular blockers are often used for paralysis and ventilation (1,6,12). Cyproheptadine is an orally available antihistamine with 5-HT1A and 5-HT2A receptor antagonist activity, but it may lead to orthostatic hypotension (1,5). Hyperthermia in patients with SS is secondary to muscular hyperactivity; thus, antipyretic therapy is not recommended (5,10).

Conclusions

Severe SS is a life-threatening condition caused by the abnormal accumulation of serotonin in the body, characterized by neuromuscular hyperactivity, autonomic nervous system hyperactivity, and altered mentation. SS can be caused by an overdose of a single serotoninergic drug or the combination of two or more drugs with serotoninergic activity. Opioids have a range of adverse effects that are well-known and studied, including histamine release, and hypersensitivities, but the serotonergic effects of some of these drugs have only recently been emphasized. The increasing use of opioids and psychiatric medicines in patients suggests that co-administration will continue. It is also imperative to carefully evaluate patient history for use of other serotonergic agents including monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), and non-prescribed agents such as herbal medications, and St. John's wort. SS is commonly self-limited and typically appears soon after the serotoninergic drug is administered, but it can occur at any time during a patient's care. While SS can occur in the setting of general anesthesia, the incidence of severe SS during general anesthesia is relatively rare. Furthermore, the recognition of SS during general anesthesia can be challenging as it can mimic other serious syndromes. For this reason, it is important for anesthesiologists to maintain a heightened awareness of the possibility of SS occurrence during general anesthesia. Treatment for SS involves discontinuing the offending drug(s) and providing supportive care for the symptoms that arise.

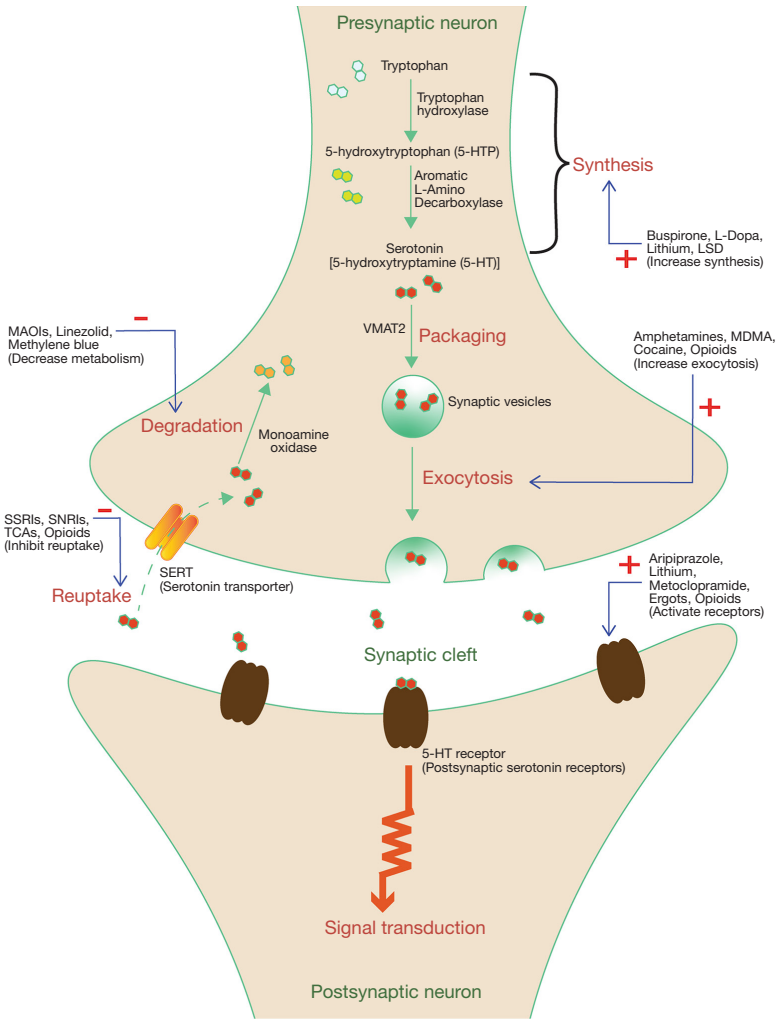

Figure 1 Mechanisms by which medications increase intrasynaptic levels of serotonin. Serotonin is synthesized from tryptophan in presynaptic neurons and packaged into presynaptic vesicles by VMAT2. When these vesicles undergo exocytosis, serotonin is released into the synaptic cleft to bind to the serotonin receptors on postsynaptic neurons. Serotonin is removed from the synaptic cleft by SERT, which takes it from the synaptic cleft back into presynaptic nerve terminals and subsequently broken down by MAO in the presynaptic neuron. LSD, lysergic acid diethylamide; VMAT2, vesicular monoamine transporter 2; MDMA, 3,4-methylenedioxymethamphetamine; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; SERT, serotonin transporter; MAO, monoamine oxidase; 5-HT, 5-hydroxytryptamine.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://amj.amegroups.com/article/view/10.21037/amj-22-44/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://amj.amegroups.com/article/view/10.21037/amj-22-44/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved. All procedures performed in this case report were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). The authors obtained written Health Insurance Portability and Accountability Act (HIPAA) authorization from the patient for the publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

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