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CASE REPORTS / CASE SERIES

Serotonergic medications, herbal supplements, and perioperative serotonin syndrome

Médicaments sérotoninergiques, suppléments à base de plantes médicinales et syndrome sérotoninergique périopératoire

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Abstract

Purpose *Perioperative use of serotonergic agents increases the risk of serotonin syndrome. We describe the occurrence of serotonin syndrome after fentanyl use in two patients taking multiple serotonergic agents.*

Clinical features *Two patients who had been taking multiple serotonergic medications or herbal supplements (one patient taking fluoxetine, turmeric supplement, and acyclovir; the other taking fluoxetine and trazodone) developed serotonin syndrome perioperatively when undergoing outpatient procedures. Both experienced acute loss of consciousness and generalized myoclonus after receiving fentanyl. In one patient, the serotonin syndrome promptly resolved after naloxone administration. In the other patient, the onset of serotonin syndrome was delayed and manifested after discharge, most likely attributed to the intraoperative use of midazolam for sedation.*

Conclusion *Even small doses of fentanyl administered to patients taking multiple serotonergic medications and herbal supplements may trigger serotonin syndrome. Prompt reversal of serotonin toxicity in one patient by naloxone illustrates the likely opioid-mediated pathogenesis of serotonin syndrome in this case. It also highlights that taking serotonergic agents concomitantly can produce the compounding effect that causes serotonin syndrome. The delayed presentation of serotonin syndrome in the patient who received a large dose of midazolam suggests that outpatients taking multiple serotonergic drugs who receive benzodiazepines may require longer postprocedural monitoring.*

Résumé

Objectif *L'utilisation périopératoire d'agents sérotoninergiques augmente le risque de syndrome sérotoninergique. Nous décrivons la survenue d'un syndrome sérotoninergique suite à l'administration de fentanyl à deux patients prenant plusieurs agents sérotoninergiques.*

Éléments cliniques *Deux patients prenant plusieurs médicaments sérotoninergiques ou suppléments à base de plantes médicinales (l'un de la fluoxétine, un supplément de curcuma et de l'acyclovir; l'autre de la fluxoétine et du trazodone) ont souffert d'un syndrome sérotoninergique en période périopératoire alors qu'ils subissaient des interventions en clinique ambulatoire. Les deux patients ont subi une perte aiguë de conscience et une myoclonie généralisée après avoir reçu du fentanyl. Chez un patient, le syndrome sérotoninergique s'est rapidement résolu suite à l'administration de naloxone. Chez l'autre, l'apparition du syndrome sérotoninergique a été retardée et ne s'est manifestée qu'après le congé de la clinique; le syndrome était probablement attribuable à l'utilisation peropératoire de midazolam pour la sédation.*

Conclusion *Même de faibles doses de fentanyl administrées aux patients prenant plusieurs médicaments sérotoninergiques et suppléments à base de plantes médicinales peuvent déclencher un syndrome*

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sérotoninergique. La neutralisation rapide de la toxicité sérotoninergique chez un patient à l'aide de naloxone illustre la pathogenèse probablement médiée par des opioïdes du syndrome sérotoninergique dans ce cas. Cela souligne également que la prise concomitante d'agents sérotoninergiques peut avoir un effet cumulatif qui provoque un syndrome sérotoninergique. La présentation retardée du syndrome sérotoninergique chez le patient ayant reçu une importante dose de midazolam suggère que les patients en clinique externe prenant plusieurs médicaments sérotoninergiques et recevant des benzodiazépines pourraient nécessiter un monitorage prolongé après leur intervention.

Contemporary antidepressants increase the neuronal concentration of serotonin (5-hydroxytryptamine [5-HT]) by affecting its production, release, or breakdown.[1] Serotonin released in the neuronal synaptic cleft is cleared through two major mechanisms: reuptake into presynaptic neurons and metabolism by monoamine oxidase-A into 5-hydroxyindoleacetic acid. Antidepressants of the selective serotonin reuptake inhibitor (SSRI) or monoamine oxidase inhibitor (MAOI) categories increase the concentration of serotonin in the synaptic cleft, which, in turn, increases neurotransmission. Excessive accumulation of serotonin in the synaptic cleft may result in neuronal overstimulation, which results in serotonin syndrome. The intensity of the signs and symptoms may vary, but fully developed serotonin syndrome is characterized by changes in mental status (anxiety, confusion, agitation, hypomania), autonomic stimulation (diaphoresis, hyperthermia, tachycardia, hypertension, mydriasis), increased muscle tone, rigidity, generalized hyperreflexia, and myoclonus in both upper and lower extremities.[1-4]

The use of antidepressants has increased in the past decade. The National Health and Nutrition Examination Survey, based on 37,959 non-institutionalized adults in the United States, reported an increase (6.8-13%) in the use of antidepressants from 1999-2012.[5] The primary mechanism of several of the most popular antidepressants used in North America is to increase serotonin levels; consequently, anesthesiologists are now more likely to encounter patients taking these medications, and the potential for encountering a patient with perioperative serotonin syndrome may be increased. In addition to the high proportion of the population taking multiple serotonergic antidepressants, herbal and other dietary supplements are currently used by one in five US adults.[6] Many ingest these substances, which are known to exert serotonergic activity, in order to improve depression (e.g., St. John's wort)[7] or mood and sleep (e.g., L-Tryptophan).[8] Serotonin syndrome can be induced as a result of excess serotonin stimulation, especially when these substances are combined with other serotonergic drugs. Turmeric, an additive used in both herbal medications and food preparations, has serotonergic activity, but descriptions are lacking in the clinical setting of serotonin syndrome. The main biologically active component of turmeric is curcumin,[6] which has garnered attention for the treatment of depression.[9,10] Its antidepressant effects are mediated through the release of serotonin and dopamine. When combined with antidepressants that increase serotonin, curcumin potentiates the brain levels of serotonin through additional action on 5-$HT_{1A/1B}$ and 5-HT_{2C} receptors.[11-13] Many healthcare providers may not be conversant with the serotonergic properties of widely used antidepressants, herbal supplements, and food additives,[14] which can result in diagnostic and therapeutic conundrums when serotonin syndrome occurs.

For anesthesiologists caring for patients who have been ingesting serotonergic medications, herbs, and food additives preoperatively, potential perioperative problems may be exacerbated by the use of fentanyl (or other opioids). Fentanyl exerts its own serotonergic action through 5-HT_{1A} receptors (Figure). Although its effects are mediated through enhancement of serotonin release and weak inhibition of serotonin reuptake,[15-17] reports that associate fentanyl by itself with serotonin syndrome are lacking.[18] In this report, we describe two cases of serotonin syndrome associated with fentanyl administration in patients preoperatively taking serotonergic antidepressants (and, in one patient, turmeric supplements).

Case series

The Mayo Clinic Institutional Review Board waived permission and patient consent for publishing information regarding single case(s) with non-identifiable characteristics (January 20, 2017). Both patients provided written permission for the use of clinical information and/or video material.

Case 1

A 72-yr-old male (weight, 68 kg; height, 170 cm) was admitted to an outpatient facility for bone marrow biopsy under monitored anesthesia care. His pertinent medical history included hypertension, atrial fibrillation, and depression. His daily medications included acyclovir 400 mg (recent history of herpes zoster), digoxin 125 μg,

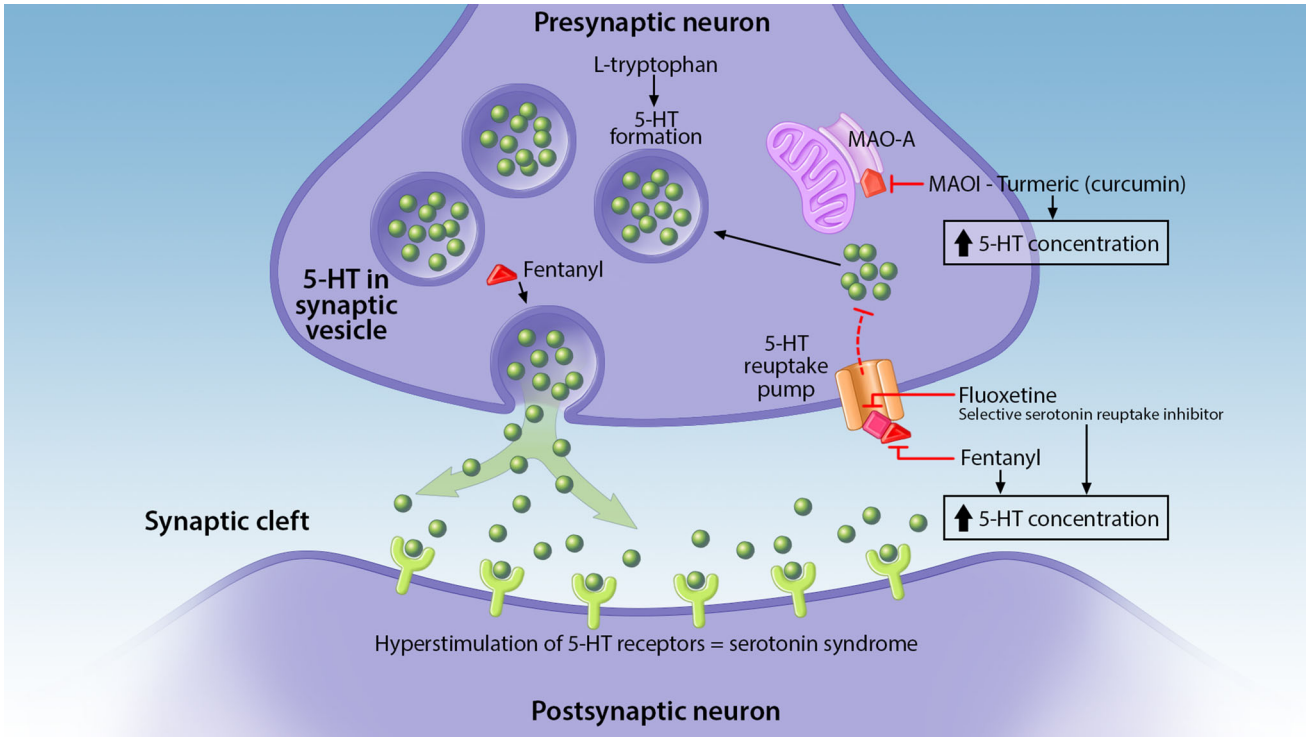

Figure Illustration depicting the effects of a serotonergic medication (fluoxetine), an herbal supplement (turmeric), and a synthetic opioid (fentanyl) on the production, reuptake, and breakdown of serotonin (5-hydroxytryptamine [5-HT]) at the neuronal synapse. Fluoxetine, a selective serotonin reuptake inhibitor, prevents reuptake of 5-HT from the synaptic cleft into the presynaptic neuron by blocking the 5-HT reuptake pump, thereby limiting any decrease in its concentration in the synaptic cleft. Turmeric acts as a monoamine oxidase A (MAO-A) inhibitor (MAOI), which decreases the breakdown of 5-HT in the presynaptic neuron and further increases its availability for subsequent release into the synaptic cleft. Fentanyl has two unique serotonergic properties: stimulating the release of serotonin from the presynaptic neuron and weakly inhibiting serotonin reuptake by the 5-HT reuptake pump in the synaptic cleft. When high concentrations of serotonin accumulate in the synaptic cleft, it can lead to hyperstimulation of the postsynaptic neuron's 5-HT receptors and, if sufficiently stimulating, the development of the symptoms of serotonin syndrome. (An animated version of the events in this Figure is shown in Supplemental Video 2; used with permission of Mayo Foundation for Medical Education and Research)

fluoxetine 40 mg, lisinopril 20 mg, metoprolol 100 mg, rivaroxaban 10 mg, and turmeric 400 mg. All of these medications have serotonergic effects (Table 1). Before the procedure, two doses of fentanyl 50 µg *iv* were administered three minutes apart. Immediately after the second dose, the patient became unresponsive and exhibited generalized seizure-like activity, with rolled eyes and clenched teeth. These signs persisted despite administration of midazolam 2 mg. A noninvasive blood pressure measurement could not be obtained because of profound muscle activity, but his pulse was strong at 120 beats·min^{-1}. A face mask with oxygen was applied, and his oxyhemoglobin saturation remained above 92%.

The supervising anesthesiologist, who had encountered a patient with serotonin toxicity in the recent past,[19] thought that these signs most likely indicated serotonin syndrome based on the cumulative serotonergic effects of fluoxetine, acyclovir, turmeric, and fentanyl. Since fentanyl was the only medication on this list that could promptly be reversed, a single 80-µg *iv* dose of naloxone was administered. Within one minute, the seizure-like activity ceased and the patient promptly regained consciousness. Even though he appeared confused and fatigued, he was fully oriented and able to respond to questions. He did not remember the preceding event. At this time, his neurologic examination and his electrolyte and glucose levels were considered normal. He remained symptom free for several hours and was discharged home. His bone marrow biopsy was performed uneventfully the following day using local anesthesia without sedation.

Case 2

A 19-yr-old male (weight, 89 kg; height, 190 cm) with a history of major depression and panic attacks underwent an outpatient dental procedure under sedation with monitored anesthesia care. His daily medications included pantoprazole 50 mg, fluoxetine 40 mg, and trazodone 50 mg, all of which have serotonergic effects (Table 1). He was extremely anxious and restless preoperatively and required sedation

Table 1 Prescription and over-the-counter drugs associated with serotonin syndrome

Class of Medication/Supplement	Generic and Trade Names
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram (Celexa), fluoxetine (Prozac, Sarafem), fluvoxamine, paroxetine (Paxil), and sertraline (Zoloft)
Serotonin and norepinephrine reuptake inhibitors (SNRIs)	Trazodone, duloxetine (Cymbalta), and venlafaxine (Effexor)
Antidepressant and tobacco-addiction medication	Bupropion (Wellbutrin, Zyban)
Tricyclic antidepressants	Amitriptyline and nortriptyline (Pamelor)
Monoamine oxidase inhibitors (MAOIs)	Antidepressants such as isocarboxazid (Marplan) and phenelzine (Nardil)
Antimigraine medications	Triptans (Axert, Amerge, Imitrex), carbamazepine (Tegretol), and valproic acid (Depakene)
Proton-pump inhibitors	Lansoprazole (Prevacid), omeprazole (Prilosec), and pantoprazole (Protonix)
Pain medications	Opioid with codeine (Tylenol with codeine), fentanyl (Duragesic), hydrocodone meperidine (Demerol), oxycodone (OxyContin, Percocet, Percodan), and tramadol (Ultram)
Angiotensin-converting enzyme (ACE) inhibitors	Benazepril (Lotensin), lisinopril (Zestril), enalapril (Vasotec), and captopril (Capoten)
Cardioselective β-adrenergic blocking drugs	Atenolol (Tenormin), metoprolol (Lopressor), bisoprolol (Zebeta), and esmolol (Brevibloc)
Digitalis glycoside	Digoxin (Lanoxin)
Mood stabilizer	Lithium (Lithobid)
Illicit drugs	LSD, Ecstasy, cocaine, and amphetamines
Herbal supplements	St. John's wort, ginseng, turmeric, and nutmeg
Over-the-counter cough and cold medications	Containing dextromethorphan (Delsym, Mucinex DM)
Non-prescription product sold online as a weight-loss agent	Sibutramine (Meridia)
Supplement often used to improve mood or sleep	L-Tryptophan
Anti-nausea medications	Granisetron, metoclopramide (Reglan), droperidol (Inapsine), and ondansetron (Zofran)
Antibiotic	Linezolid (Zyvox)
Factor Xa inhibitor oral anticoagulant	Rivaroxaban (Xarelto)
Antiviral medications	Ritonavir (Norvir) and acyclovir (Zovirax)

Data from Serotonin syndrome: symptoms and causes. Available at: http://www.mayoclinic.org/diseases-conditions/serotonin-syndrome/symptoms-causes/dxc-20305673

with intravenous midazolam 5 mg, propofol 240 mg, and fentanyl 100 μg. Immediately after the 45-min dental procedure, he followed commands and transferred himself from the operating table to a recovery chair. He remained lucid, and after he was appropriately oriented (30 min later) in the recovery room, his intravenous catheter was removed. Shortly thereafter, however, he became anxious and appeared agitated, similar to his preoperative demeanour. His father remarked that this was his regular state of behaviour; thus, he was transported by wheelchair to the hospital entrance for dismissal.

Just before this patient was transferred to the car, however, his entire body acutely started shaking and he became unresponsive. He was urgently returned to the postoperative care area where he was unresponsive and continued to exhibit generalized muscle jerking, eye fluttering, nystagmus, and head turning to the right. His heart rate was 105 beats·min^{-1}, blood pressure was 130/70 mmHg, and oxyhemoglobin saturation was 100% on room air. He was given supplemental oxygen via nasal cannula and intravenous access was re-established. Within two minutes, the abnormal movements subsided, and he was able to nod his head to questions. Three minutes later, however, he again became unresponsive with the same pattern of eye fluttering and muscle jerking. He was then given midazolam 2 mg, which quickly halted these symptoms. He was transferred to the emergency department for further treatment and evaluation. During monitored transport, the patient once again became unresponsive, had irregular eye movements, and exhibited irregular and asymmetric myoclonic activity in both upper and lower extremities (Video 1, available as Electronic Supplementary Material). He was given lorazepam 4 mg intravenously, which resulted in gradual improvement of these symptoms. Once his myoclonic movements subsided, he was able to follow commands and

appropriately respond to questions. He reported no recollection of these events. During one of the spells, a neurologist performed rapid electroencephalography at the bedside, which showed no epileptic activity. His symptoms subsided over the next three hours and he was discharged home.

Discussion

Our cases illustrate the increased risk of perioperative serotonin syndrome in patients taking multiple serotonergic medications and herbal supplements when fentanyl is used during procedures. In the first patient, serotonin syndrome developed immediately after fentanyl administration and resolved promptly by treatment with naloxone. This suggests that fentanyl may have compounded the serotonergic effects of this patient's various daily medications, including antidepressants and turmeric herbal supplements. In the second patient, the presentation of serotonin syndrome was delayed after the administration of fentanyl, possibly because of a concomitantly administered large dose of midazolam. It is plausible that both patients had high but asymptomatic preoperative levels of neuronal serotonin and became symptomatic only after the administration of fentanyl increased their serotonin levels sufficiently high to induce myoclonus.

The mechanism of neurotransmission for serotonin and its compounding effects on the development of serotonin syndrome are depicted in Video 2 (available as Electronic Supplementary Material). This compounding drug effect is supported by the observation that the apparent serotonin syndrome in the first patient was resolved promptly after antagonism of fentanyl with naloxone. In our view, the delayed serotonin toxicity in the second patient could be explained by the high dose of midazolam used for sedation. Midazolam and other benzodiazepines have been used for treatment of serotonin syndrome because they increase the threshold for myoclonus.[20] The administration of midazolam during the sedation of this patient could have prevented an earlier manifestation of serotonin syndrome. In retrospect, this patient's unusual perioperative anxiety and restlessness and the need for excessive sedation may have been unrecognized signs of increased serotonergic activity. This patient did not receive naloxone because serotonin syndrome was not initially considered in the differential diagnosis, and the anesthesia provider did not make an association between fentanyl and the myoclonic event. Both clinical scenarios provide a cautionary tale regarding the safety of concomitant use of multiple serotonergic medications in the perioperative period and highlight the need for an in-depth review of preoperative medications in patients undergoing anesthesia.

Diagnosis of serotonin syndrome is based on presenting signs and symptoms in patients taking serotonergic medications. No blood test is available to confirm or refute the diagnosis. Serotonin toxicity is typically diagnosed on the basis of the Hunter Serotonin Toxicity Criteria (Table 2).[3] The most important aspect for diagnosis is familiarity with the existence of this syndrome in patients already using serotonergic medications. One earlier epidemiologic survey showed that 85% of physicians are not aware of this clinical diagnosis,[14] even though it may occur in 14-16% of those with SSRI overdose.[4]

Signs of mild serotonin toxicity may be subtle or may be confused with preoperative anxiety, as demonstrated by the second patient who exhibited unusual restlessness and anxiety. The differential diagnosis for serotonin toxicity includes conditions such as neuroleptic malignant syndrome, seizures, anticholinergic delirium, sympathomimetic toxicity, and malignant hyperthermia.[4] Nevertheless, generalized spontaneous clonus, as was seen in both of our patients, is rare in conditions other than serotonin syndrome.[3]

Our cases highlight concerns regarding simultaneous use of multiple serotonergic medications. Furthermore, they call attention to the possible risks of taking serotonergic herbal supplements with antidepressant medications, especially during perioperative care. In this specific case, curcumin (in turmeric) may have potentiated the serotonergic effects of the patient's antidepressants and

Table 2 Decision rules for predicting serotonin toxicity

In the presence of a serotonergic agent:

1. IF (spontaneous clonus=yes) THEN serotonin toxicity=YES
2. ELSE IF (inducible clonus=yes) AND [(agitation=yes) OR (diaphoresis=yes)] THEN serotonin toxicity=YES
3. ELSE IF (ocular clonus=yes) AND [(agitation=yes) OR (diaphoresis=yes)] THEN serotonin toxicity=YES
4. ELSE IF (tremor=yes) AND (hyperreflexia=yes) THEN serotonin toxicity=YES
5. ELSE IF (hypertonic=yes) AND (temperature >38°C) AND [(ocular clonus=yes) OR (inducible clonus=yes)] THEN serotonin toxicity=YES
6. ELSE serotonin toxicity=NO

Reproduced with permission from: *Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM.* The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. QJM 2003; 96: 635-42[3]

other medications.[12,13] For example, this patient was taking acyclovir, a serotonergic agent that can decrease the conversion of serotonin to 5-hydroxyindoleacetic acid,[21] as well as digoxin, which is also implicated in the pathogenesis of serotonin syndrome (Table 1). The second patient was taking pantoprazole, a proton-pump inhibitor that inhibits cytochrome CYP2C19, an enzyme that is important in SSRI metabolism. In retrospect, this patient should probably have been on a lower dose of SSRI medications.[22]

Anesthetic recommendations for patients on SSRIs

Anesthesiologists must consider the compounding serotonergic effect of fentanyl (and other opioids) when it is administered to patients taking serotonergic medications and herbal supplements.[18] In a review by Rastogi *et al*., the authors detail the effects of opioids on the pathogenesis of serotonin syndrome.[18] Table 1 outlines medications and herbal supplements that are serotonergic, including those commonly used in anesthesia practice. For example, the use of MAOI medications and compounds that have MAOI effects (e.g., methylene blue) should be avoided in patients taking SSRIs. The US Food and Drug Administration has issued this warning and has suggested the discontinuation of SSRIs before elective operations anticipated to require methylene blue.[19,23] The timing of SSRI discontinuation is based on the clearance rates of individual medications. Specifically, the half-life of fluoxetine, the longest-acting SSRI, is two to six days, and the half-life of its active metabolite, norfluoxetine, is seven to 15 days. In contrast, other commonly used SSRIs and their active metabolites have shorter half-lives: paroxetine, 21 hr; sertraline, 26 hr; and citalopram, 33 hr.[24] Because of the long half-life of fluoxetine, up to five weeks is needed for its full elimination.

All opioids have been implicated in triggering serotonin syndrome, although the phenanthrene morphine analogues (e.g., hydromorphone, oxymorphone, and buprenorphine) do not act as direct SSRIs.[16] These three opioids may, however, increase intrasynaptic serotonin levels, either through increased release of neurotransmitters or by a yet unknown mechanism.[18]

Because of the potentially life-threatening consequences of serotonin toxicity,[4,25] it is critical to be familiar with its signs and symptoms and to have a high index of suspicion for perioperative serotonin syndrome. If it occurs, administration of naloxone, as in our first patient, should be considered. Of course, naloxone administration may be problematic in the perioperative setting because of acute reversal of analgesia and its own complications. In such cases, after weighing risks *vs* benefits, the administration of naloxone should be preceded by the use of non-serotonergic analgesics (e.g., ketorolac, acetaminophen, local anesthetic infiltration of the surgical field, or dexmedetomidine).[20] Ketamine has antidepressant activity that is thought to be mediated via a serotonin-dependent mechanism,[26,27] so it may be prudent to avoid using it for this purpose. Nevertheless, there is a lack of case reports associating ketamine with serotonin syndrome.

Conclusion

The clinical scenarios presented here suggest that even small doses of fentanyl in patients taking multiple serotonergic medications or herbal supplements may be associated with the development of serotonin syndrome. Reversal with naloxone may resolve this problem. If benzodiazepines are used for sedation, serotonin toxicity may be masked and the onset of serotonin syndrome may be delayed. Anesthesiologists must understand which medications and herbal supplements are serotonergic, and they must have a heightened awareness for detecting signs of serotonin syndrome during the perioperative period.

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