Serotonin syndrome is an unexpected adverse reaction of serotonergic medication. Some drugs used by anesthesiologists may cause serotonin syndrome. Serotonin syndrome is known to be related to 5-hydroxytryptamine 1A and 5-hydroxytryptamine 2A agonism. However, recent research has revealed evidence that 5-hydroxytryptamine 3 (5-HT3) antagonism can also play a role in serotonin syndrome. Among the 5-HT3 antagonists, palonosetron is the most highly specific. In this study, we present the first case of fentanyl- and meperidine-induced serotonin syndrome precipitated by palonosetron in general anesthesia. (Anesth Pain Med 2015; 10: 267-270)

Key Words: Fentanyl, Meperidine, Palonosetron, Serotonin, Serotonin syndrome.

In this study, we present the first case of fentanyl- and meperidine-induced SS precipitated by palonosetron in general anesthesia.

CASE REPORT

An emergency appendectomy for acute appendicitis was performed in a 51-year-old male. Preoperatively, he had been treated with losartan, thiazide, and atorvastatin for hypertension and hyperlipidemia for years. He had no other medication, including a serotonergic agent, for at least two months before admission. He had received lumbar discectomy 10 years prior and had no known lifetime history of allergies, shock, or perioperative event. His physical status classification was American Society of Anesthesiologists physical status Classification II. His electrocardiogram, laboratory tests, and preoperative vital signs were unremarkable. About 8 and 7 h before the onset of SS, 50 mg tramadol was injected at each time to control pain from appendicitis. No other potentially serotonergic agent was administered before surgery.

On the day of surgery, preoperative vital signs were blood pressure of 100/60 mmHg, heart rate of 82 beats/min, pulse oxygen saturation of 97% on room air, respiratory rate of 13 breaths/min, and body temperature through the tympanic membrane of 36.7°C.

General anesthesia was induced with 2 mg/kg propofol, 1 μg/kg fentanyl, and 0.6 mg/kg rocuronium. After tracheal intubation, anesthesia was maintained with 6% desflurane and 50% nitrous oxide in oxygen. Palonosetron was administered 5 min after induction to prevent postoperative nausea and vomiting. The patient was hemodynamically stable until surgery was done uneventfully. His body temperature through the esophagus
was 36.6–36.7°C. End-tidal carbon dioxide was maintained between 30 and 35 mmHg during surgery.

Neuromuscular block was reversed by 0.2 mg glycopyrrolate and 10 mg pyridostigmine. A tracheal tube was extubated. The patient being able to lift his head for 5 s and sustaining a hand grip for 5 s ensured no residual neuromuscular blockade. The total operating time was about 30 min. After confirming full recovery from neuromuscular blockade and with an alert mental status, the patient was transferred to the post-anesthetic care unit.

In the post-anesthetic care unit, the patient did not complain of any postoperative nausea and vomiting (PONV) or pain, his mental status was alert, his vital signs were normal, and his visual analogue scale was 3 for about 30 min. Intravenous meperidine of 25 mg was administered to the patient when he had mild shivers. Immediately after the injection of meperidine, the shivering that seemed like a clonus exacerbated rather than subsided, and the patient showed diaphoresis and agitation. Moreover, his mental status became drowsy and confused. Tachypnea and fever (38.8°C) were determined at that time. SS was suspected, and immediate supportive management that included tepid massage and rapid intravenous ice-cold normal saline (500 ml/h) was conducted. Nevertheless, the patient’s body temperature reached 39.2°C. His blood pressure reached 182/94 mmHg, and his maximal heart rate was 120 beats/min. Oxygen saturation was low at 94% on the 6 L/min O₂ reserve bag. Respiration was shallow and as fast as 26 breaths/min. ABGA was checked (pH 7.382, PCO₂ 39.6 mmHg, PO₂ 82.2 mmHg, HCO₃⁻ 23.0 mM/L, and O₂ saturation 96%), and his blood sugar was normal. To control hypertension, 2.5 mg labetalol and 1 mg nicardipine were injected. Cyproheptadine, a 5-HT antagonist, was considered, but it was not administered because of the patient’s poor cooperation due to confused mentality. The patient’s mental status, vital signs, and accompanying symptoms, such as agitation and diaphoresis, gradually recovered 3 h after the onset of SS (Fig. 1). His vital signs were blood pressure of 120/80 mmHg, heart rate of 80 beats/min, respiratory rate of 20 breaths/min, and body temperature through the tympanic membrane of 36.5°C. After the patient recovered, he was transferred to the general ward from the post-anesthetic care unit. No more potentially serotonergic agent and palonosetron were administered since SS occurred.

In the general ward, the patient did not complain of any PONV. Acetaminophen and ketorolac were administrated for his pain. He was eventually discharged without any complications and sequelae.

**DISCUSSION**

Serotonin is a neurotransmitter involved in mood, personality, emesis, appetite, pain perception, sexual behavior, temperature regulation, hormone regulation, and wakefulness [4]. SS is a toxic state resulting from the increased serotonergic neurotransmission in the postsynaptic neuron [5]. Serotonin toxicity generally occurs in patients who have ingested drug combinations that synergistically increase synaptic serotonin or have taken one medication in a high dose [5]. Monoaminergic neurotransmitters, N-methyl-d-aspartate receptor antagonists, and γ-aminobutyric acid have also been suggested to affect SS development, and they provide evidence that other neurotransmitters may also play a role [4]. A large number of medications, antidepressants, opioids, and central nervous system stimulants, among others, can cause SS (Table 1) [4].

The symptoms of SS are akathisia, tremor, altered mentality, clonus, muscular hypertonicity, and hyperthermia. The symptoms are specific and have a wide spectrum from mild to life threatening.

No laboratory test can confirm SS. Therefore, diagnosis is conducted through the evaluation of symptoms and patient’s history. Sternbach’s Serotonin Toxicity Criteria [6] are the first strictly evaluated standard. Sternbach’s Serotonin Toxicity Criteria [6] for SS are as follows: (1) recent addition of a serotonergic agent, (2) absence of other possible etiologies, (3)
Table 1. Drugs Associated with Serotonin Syndrome

| Antidepressants                                                                 |
|--------------------------------------------------------------------------------|
| Bupropion, nefazodone, trazodone, mirtazapine, tapentadol, monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors |

| Opioids                                                                 |
|------------------------------------------------------------------------|
| Tramadol, meperidine, fentanyl, pentazocine, buprenorphine, oxycodone, hydrocodone |

| Central nervous system stimulants                                      |
|-----------------------------------------------------------------------|
| 3,4-Methylenedioxyamphetamine, phentermine, diethylpropion, amphetamine, cocaine, sibutramine, methylphenidate, methamphetamine |

| 5-HT3 agonists                                                      |
|---------------------------------------------------------------------|
| Triptans                                                           |
| Psychedelics                                                       |
| 5-Methoxy-diisopropyltryptamine, lysergic acid diethylamide         |
| Herbs                                                              |
| St John's wort, Syrian rue, Panax ginseng, nutmeg, yohimbe          |
| Others                                                             |
| Tryptophan, L-Dopa, valproate, buspirone, lithium, linezolid, dextromethorphan, ritalin, chlorphenteramine, 5-hydroxytryptophan, risperidone, olanzapine, ondansetron, granisetron, metoclopramide |

Table 2. The Hunter Serotonin Toxicity Criteria: Decision Rules

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

no recent addition or increase in neuroleptic agent, and (4) at least three of the hyper-serotonergic symptoms (i.e., confused mentality, agitation, diaphoresis, shivering, and fever in this case).

The Hunter Serotonin Toxicity Criteria (Table 2) were developed later on. They have better sensitivity (69–84%) and specificity (94–97%) than Sternbach’s Serotonin Toxicity Criteria [5].

The patient’s symptoms satisfied both Sternbach’s Serotonin Toxicity Criteria [6] and the Hunter Serotonin Toxicity Criteria because he showed clonic movement [5]. The serotonergic agents possibly implicated in SS were palonosetron, tramadol, fentanyl, and meperidine in this patient. The influence of tramadol on SS was doubtful because the interval of tramadol medication and the onset of SS was more than 6 h, the half-life of tramadol. However, the timing of the meperidine injection was closely related to the onset of SS. Moreover, the onset of SS was in time with the duration of fentanyl and palonosetron. Therefore, we conclude that SS was associated with the administration of fentanyl, palonosetron, and meperidine.

Phenylpiperidine opioids (i.e., fentanyl, sufentanyl, alfentanil, and meperidine) will have weak serotonergic activity by blocking the presynaptic serotonin reuptake [13]. A case was reported of only meperidine inducing SS [6]; in this case, the patient had susceptibility to SS. Conversely, most previous cases and an original research indicate that meperidine-induced SS is almost always precipitated by other serotonergic agents [9-11].

In the current case, palonosetron was the most likely precipitating agent of fentanyl- and meperidine-induced SS due to the correspondence between the timing of its administration and the onset of symptoms. SS occurrence by coadministration of phenylpiperidine opioids has not yet been reported in the literature. The patient’s symptom started with the meperidine injection in time with the duration of palonosetron.

This case is the first one related to palonosetron. The case suggests that selective 5-HT3 antagonism by palonosetron can precipitate SS induced by meperidine in anesthesia. Palonosetron is related to a low rate of adverse events because of its high selectivity in 5-HT3 receptors, and its usage is expanding in perioperative settings. Therefore, anesthesiologists should be aware of and prepare for the possible incidence of SS when palonosetron, fentanyl, and meperidine are combined during anesthesia.

The theoretical mechanism of SS precipitation by 5-HT3 selective antagonism is that increased serotonin in the synapse by blocking 5-HT3 may enhance the binding in the 5-HT1 and 5-HT2 receptors. An alternative explanation is the competitive inhibition of the metabolism of meperidine and fentanyl by palonosetron. Palonosetron, fentanyl, and meperidine mainly metabolize in the liver through the cytochrome P450 hepatic enzyme. Palonosetron may elevate the plasma concentration of meperidine and fentanyl by disturbing the elimination through the cytochrome P450 hepatic enzyme. Further studies to identify the mechanism in this case and to discover the role of 5-HT3 antagonism in SS are necessary.

Moreover, palonosetron shows a prolonged therapeutic effect
by causing 5-HT₃ receptor internalization [12]. The effect of a single dose of palonosetron can persist for more than 40 h. Discontinuing all possible causative agents is the key to reverse SS immediately. However, the discontinuation of palonosetron is not enough to prevent SS recurrence. As shown in our case, the combined use of perioperative palonosetron, fentanyl, and meperidine should be carefully monitored until the effect of palonosetron dissipates. Moreover, alternative non-serotonergic agents to fentanyl and meperidine should be considered when palonosetron is chosen for the prevention or treatment of perioperative nausea and vomiting. In this case, no further serotonergic agent should be administered until the elimination half-life of palonosetron has passed to prevent possible SS recurrence.

The treatment for all forms of serotonin toxicity involves supportive care and cessation of any serotonergic medication. Severe serotonin toxicity or serotonin crisis is a medical emergency, and initial management must focus on airway, breathing, and circulation. Supportive care, including passive and active cooling of the patient, sedation with benzodiazepines, intubation, and muscle paralysis, must take precedence over any specific pharmacological treatment. If benzodiazepines and supportive care fail to improve agitation and correct the vital signs, antidotal therapy with cyproheptadine is suggested [13]. SS is known to be related to 5-HT₁A and 5-HT₂A agonism. Cyproheptadine is a histamine-1 receptor antagonist with nonspecific 5-HT₁A and 5-HT₂A antagonist properties [13]. Cyproheptadine is only available in oral form, but the patient’s mental confusion made its oral administration impossible. Nevertheless, cyproheptadine may be crushed and given through a nasogastric or orogastric tube.

Although conservative treatment was successful, the immediate recognition and the intensive supportive care were vital in this case.

In conclusion, we present the first case of the precipitation of probable fentanyl- and meperidine-induced SS precipitated by palonosetron in general anesthesia. Anesthesiologists should be careful in the concomitant use of palonosetron, fentanyl, and meperidine and should monitor the incidence of SS in perioperative anesthesia and analgesia.

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