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A suspected case of serotonin syndrome induced by palonosetron and ramosetron administration

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Serotonin syndrome occurs when serotonin (5-hydroxytryptamine, 5-HT) levels increase and is accompanied by symptoms of mental status changes, neuromuscular abnormalities, and autonomic hyperactivity. Serotonin receptor 3 antagonists, such as palonosetron or ramosetron, are commonly used for their antiemetic effects during general anesthesia. However, overdosage of these drugs carries a risk of serotonergic toxicity as they increase serum serotonin levels due to inhibition of serotonin reuptake. Serotonin syndrome caused by 5-HT_3 antagonists is thought to be caused by the synergistic effects of high doses of serotonergic drugs or the combination of two or more serotonergic drugs with different mechanisms of action. The incidence of serotonin syndrome is unknown because it is a rare condition that cannot be selected for in randomized clinical trials. Therefore, physicians must focus on the clinical manifestations of the syndrome and manage patients before the condition becomes life-threatening.

Keywords: Serotonin syndrome, Palonosetron, Ramosetron, 5-HT_3 antagonist

INTRODUCTION

Serotonin syndrome is often described by the clinical triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities, but not all of these findings are consistently present in all patients with the disorder (Boyer and Shannon, 2005). Serotonin syndrome is a drug-induced syndrome characterized by a series of dose-related side effects resulting from increased serotonin concentrations in the central nervous system. This is also known as serotonin toxicity, as it probably covers a spectrum from mild to severe side effects, depending on the degree to which serotonin is increased (Buckley et al., 2014). It can be caused by drug interactions, some of which can be potentially fatal. Serotonin syndrome occurs when serotonin levels increase. Different drug classes and combinations work synergistically to activate the serotonergic pathway and can therefore cause serotonin syndrome. Therefore, it is important to be aware of these drugs that exhibit strong serotonergic effects during general anesthesia.

Serotonin syndrome is a life-threatening condition induced by an increase in serotonergic activity in the central nervous system. Altered mental status, neuromuscular abnormality, and autonomic hyperactivity are the typical signs of the syndrome (Scotton et al., 2019). It is also referred to as serotonin toxicity, which is diagnosed by clinical manifestations rather than the measurement of serum serotonin level. The most frequent clinical features are altered mental status, anxiety, myoclonus, hyperreflexia, sweating, tremors, and tremors. The putative pathophysiological mechanism involves brainstem and spinal cord activation of the 1A form of serotonin (5-hydroxytryptamine or 5-HT) receptors. Both men and women are affected, and patients' ages range from 20 to 68 years (Sternbach, 1991). Once treatment begins, the syndrome usually resolves within 24 hr, but confusion may persist for several days, and deaths have been reported.

There is no effective drug treatment established for serotonin syndrome (Gillman, 1999). Unfortunately, the term serotonin syndrome has many different meanings, and many people writing about this topic have been unable to distinguish between them. This has led to erroneous conclusions regarding the 5-HT recep-

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tor subtype responsible for the life-threatening effects of animal and human toxicity and suggestions for ineffective treatment strategies (Isbister and Buckley, 2005). This paper is a case report of a 79-year-old woman suspected of having serotonin syndrome after receiving palonosetron and ramosetron.

MATERIALS AND METHODS

A 79-year-old female patient (152 cm, 58 kg) was hospitalized one day before total knee arthroplasty due to bilateral osteoarthritis. Her patient had a history of hypertension and she was receiving aspirin and clopidogrel for unstable angina. Her antithrombotic treatment was discontinued 7 days before surgery. The patient had no cardiac symptoms, and she had normal regional wall motion with an ejection fraction of 62% on echocardiography. The patient was additionally prescribed carvedilol, amlodipine, fimasartan, and trimetazidine to treat hypertension. The patient had a prior history of L3–5 posterior interbody fusion surgery in 2014.

In the preoperative evaluation, chest x-ray, electrocardiogram, and pulmonary function tests showed normal results, and the patient had no history of drug allergy. The patient was classified as American College of Anesthesiologists physical status class II. Due to hyponatremia (131 mEq/L), the nephrology team was consulted, and it was confirmed that the patient was eligible for surgery. Vital signs obtained immediately after admission to the theater were stable (blood pressure, 114/78 mmHg; heart rate, 80/min; oxygen saturation, 98%; temperature, 36.5°C). Glycopyrrolate (0.2 mg) and palonosetron (0.075 mg) were administered intravenously as pretreatment before inducing general anesthesia.

Propofol (1.3 mg/kg) and rocuronium (0.6 mg/kg) were administered for the initial induction. Remifentanil was continuously infused at 0.05 μg/kg/min, and the patient was intubated using a plain tube. After the intubation, invasive arterial blood pressure monitoring was applied to the left radial artery using an angio-needle. CardioQ esophageal Doppler (CardioQ-ODM, Deltex Medical, West Sussex, UK) was used to monitor cardiac index, stroke volume change, and corrected flow time. During surgery, the patient's vital signs were stable, and desflurane were used for continuous anesthesia with minimum alveolar concentration 1.0. Other physiologic signs during surgery include: systolic blood pressure >90 mmHg; oxygen saturation 100%; bispectral index 40–50; pH 7.394; pCO_2 42.2 mmHg; pO_2 276 mmHg; Na 134 mmol/L; cardiac index 2.1–2.4 L/min/m^2; stroke volume variation 11%–15%. The total anesthesia time was 2 hr and 40 min, and the patient was transferred to the postanesthetic care unit (PACU) after recovering from general anesthesia without any symptoms.

RESULTS

The patient's vital signs in the PACU were stable (blood pressure, 142/72 mmHg; heart rate, 62/min; temperature, 36.4°C). The patient's consciousness was clear and breathing was normal,

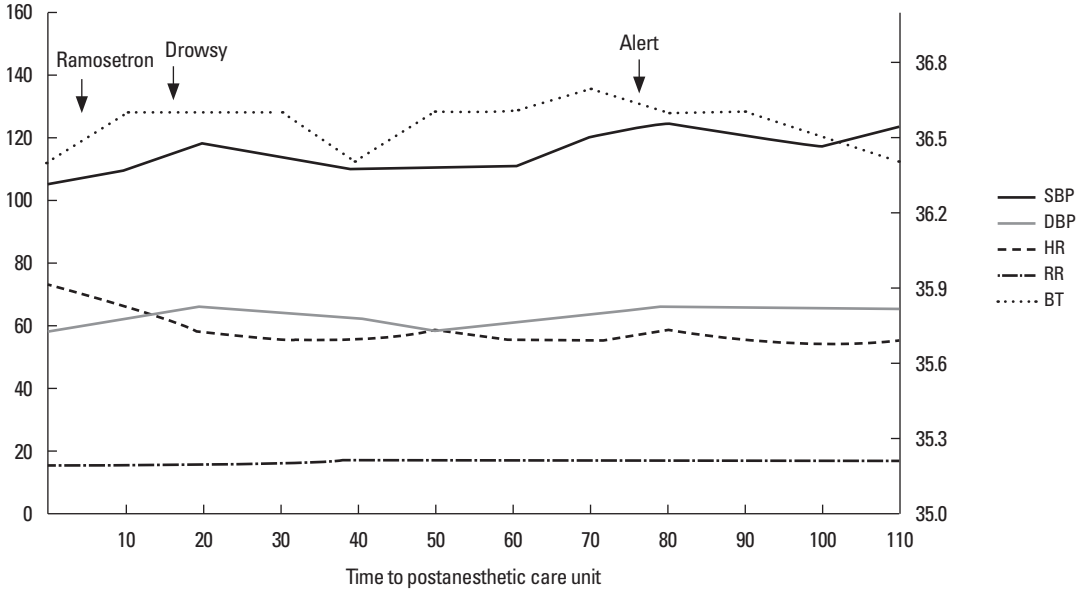

Fig. 1. The patient became drowsy, a loss of orientation in time and place, lower extremity stiffness, and was incapable of speaking, but responded to pain for an hour. SBP, systolic pressure; DBP, diastolic pressure; HR, heart rate; RR, respiration rate; BT, body temperature.

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but he complained of headache, nausea, and vomiting. Ramosetron (0.3 mg) was administered to improve the symptoms, but over time, the patient showed signs of decreased consciousness and limb stiffness (Fig. 1). Although she was disoriented to her time and place and unable to speak, she reacted to pain. The patient had lower extremity rigidity but no signs of hyperreflexia or seizures. Symptoms lasted for an hour in the treatment room. Pupil reflexes were normal, vital signs were stable, and blood sugar level was 187 mg/dL. The patient also showed no signs of high fever or shivering. Plasma solution (200 mL) was administered with oxygen supply of 6 L/min. After observation in the ward for about an hour, the patient's symptoms improved and he was transferred to a general ward. She complained of persistent headache, postoperative nausea and vomiting on the ward. To relieve her symptoms, she was given intravenous metoclopramide (10 mg). Afterwards, the patient regained her consciousness without neurological deficits. In her case she underwent a brain computed tomography (CT) to rule out infarction or other neurological problems. However, the brain CT scan was within the normal range, and a consultation with the neurology team was made for the next surgery. A week later, the patient underwent general anesthesia again for surgery on her contralateral knee, but this time she did not use palonosetron and ramosetron. Her postoperative period was uneventful.

DISCUSSION

The Sternbach criteria and Hunter criteria (Table 1) are commonly used to diagnose the condition. In our case, these criteria were not fully met. However, serotonin syndrome was suspected based on the postoperative headache and mental confusion that occurred in the postanesthesia clinic. The patient was not taking any medications that affect serotonin reuptake and had no previous medical history or other neurological deficits that could be attributed to the condition. We were unable to determine the direct cause of the mental changes. However, intravenous palonosetron may increase the risk of developing serotonin syndrome depending on symptoms in the postanesthesia care room, and co-administration with ramosetron may worsen serotonin toxicity.

Palonosetron is a 5-HT_3 receptor antagonist with a longer half-life of approximately 40 hr and is more effective than first-generation 5-HT_3 receptor antagonists. Palonosetron, the newest drug in the 5-HT_3 receptor antagonist class, differs from other drugs in its class by its higher receptor binding affinity and longer half-life. These pharmacological properties have resulted in superior antiemetic activity in clinical trials, especially in the treatment of nausea and vomiting caused by chemotherapy (De Leon, 2006). Lee et al. (2015) reported no significant differences in the overall incidence of postoperative nausea and vomiting and complete responders in the palonosetron, granisetron, and ramosetron groups. According to a meta-analysis, palonosetron was found to be less effective than ondansetron in preventing nausea and vomiting in the early postoperative period, but palonosetron was found to be more effective than ondansetron in preventing vomiting after laparoscopic surgery (Liu et al., 2018).

The longer half-life of these agents prolongs the serotonergic effects and inhibits the pathway through receptor internalization, increasing the risk of serotonin syndrome when administering other

Table 1. Comparison between the Sternbach and Hunter criteria for diagnosing serotonin toxicity

Item	Sternbach criteria	Hunter criteria
Inclusion criteria	Presence of serotonergic medication	Presence of serotonergic medication
Exclusion criteria	Presence of other possible disease etiologies (e.g., infection, substance abuse, and withdrawal) and/or recent addition (or increase in dose) of neuroleptic medication	None
Signs and symptoms	At least three of the following signs/symptoms: Mental status changes (confusion, hypomania) Agitation Myoclonus Hyperreflexia Diaphoresis Shivering Tremor Diarrhea Incoordination Fever	Any of the following combinations of primary (1°) ± secondary (2°) signs/symptoms: 1°: Spontaneous clonus alone 1°: Inducible clonus and 2°: Agitation or diaphoresis 1°: Ocular clonus and 2°: Agitation or diaphoresis 1°: Tremor and 2°: Hyperreflexia 1°: Hypertonicity and fever (temperature >38°C) and 2°: Ocular clonus or inducible clonus

serotonergic agents. Although serum serotonin levels are not considered evidence of serotonin syndrome, administration of 200 mL of plasma solution may dilute the elevated serum serotonin levels and attenuate the patient's symptoms. Since discontinuation of both drugs (palonosetron and ramosetron) in the general ward alleviated symptoms, serotonin toxicity may be considered a contributing factor to the patient's condition. Additional evidence for serotonin syndrome is that the patient did not develop serotonin syndrome symptoms during the second surgery in which neither drug was administered. There are currently no reported cases of serotonin syndrome due to metoclopramide alone, but there are cases where metoclopramide may cause serotonin syndrome due to drug interactions or intentional drug overdose (Boyer and Shannon, 2005).

Metoclopramide also contributes to serotonin syndrome by impairing reuptake from the synaptic cleft to presynaptic neurons. Therefore, caution should be exercised with serotonergic agents frequently used in general anesthesia. In addition, various drugs such as fentanyl, remifentanil, ondansetron, and tramadol have been shown to cause serotonin syndrome. The management of serotonin syndrome includes close monitoring for normal vital signs, supportive care, and discontinuation of any serotonergic agents (Isbister and Buckley, 2005).

Although our patient's symptoms were mild to moderate, severe serotonin toxicity can be a life-threatening condition. Supportive care may be initiated, including temperature monitoring, maintenance of oxygen saturation, benzodiazepine sedation, and intravenous fluids (Gillman, 1999). If muscle paralysis is confirmed, electroencephalography may be considered to evaluate seizure activity. If supportive care fails to manage vital signs, more aggressive treatment with a serotonin antagonist such as cryproheptadine may be considered (McDaniel, 2001).

In conclusion, our case report demonstrates the possibility of developing serotonin syndrome in a patient receiving preoperative palonosetron and postoperative ramosetron. Anesthesiologists should consider serotonin syndrome in elderly patients with altered mental status and should also be alert to interactions between drugs that act through the serotonergic pathway and 5-HT_3 antagonists.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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