Case Report

Serotonin syndrome manifesting as patient movement during total intravenous anesthesia with propofol and remifentanil☆,☆☆

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Abstract A patient who manifested signs of serotonin syndrome during an intravenous anesthetic with remifentanil and propofol is presented. The patient displayed lower extremity clonus, nystagmus, and diaphoresis. At the time of surgery, the patient was being treated with fluoxetine (a selective serotonin reuptake inhibitor). A presumptive diagnosis of serotonin syndrome was made intraoperatively and all opioids were discontinued. His symptoms resolved in the Postanesthesia Care Unit without incident.

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1. Introduction

Despite the increased use of proserotonergic drugs in the general population, serotonin syndrome remains a poorly recognized condition. Specific diagnosis of serotonin syndrome may be difficult due to its broad constellation of symptoms. A range of clinical findings, including mental status changes, neuromuscular abnormalities, and autonomic dysfunction, may be associated with excess serotonin activity [1]. Several drugs have been implicated in precipitating serotonin syndrome; among them, opioid analgesics are particularly relevant for anesthesiologists. A case of serotonin syndrome, which was unique in its initial manifestation as patient movement during total intravenous anesthesia (TIVA) using remifentanil and propofol, is presented.

2. Case report

Written, informed consent for publication of this report was obtained from the patient. A 23 year old man was scheduled for distal patellar realignment of the right knee. The patient was taking medications for treatment of severe depression and anxiety, including fluoxetine [a selective serotonin reuptake inhibitor (SSRI)] 60 mg/day and diazepam 10 mg at night. One hour before surgery, the patient received intravenous (IV) midazolam 2 mg for sedation during placement of an ultrasound-guided femoral...
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nerve catheter. Before catheter placement, 30 mL of 0.25% bupivacaine with 5 μg/mL of epinephrine was injected to expand the tissue plane deep to the fascia iliaca. General anesthesia was induced with propofol 150 mg and fentanyl 250 μg. After anesthetic induction, the patient was ventilated with air and oxygen through a Laryngeal Mask Airway (LMA), and anesthesia was maintained using an infusion of propofol 0.1 mg/kg/min and remifentanil 0.2 μg/kg/min. No neuromuscular blockers were used.

During sterile skin preparation, the surgeons reported patient movement. Propofol 50 mg and remifentanil 100 μg were given as a bolus with no clinical change. On closer observation, the patient’s “movement” was actually bilateral lower extremity clonus at the ankle. This was in response to manipulation of the lower extremities during sterile skin preparation and drape placement. Because this movement raised concerns about inadequate depth of anesthesia, the patient’s eyes were untaped and examined. At that time, the patient had hoarse dysarthria and diaphoresis. However, his vital signs showed no remarkable change, with a heart rate of 50-60 beats per minute and systolic blood pressure of 90 to 100 mmHg. A nasopharyngeal temperature probe showed normothermia.

The intraoperative course was remarkable only for some persistent clonus bilaterally at the ankles. A presumptive diagnosis of serotonin syndrome was made. The remifentanil and propofol were discontinued, and no additional opioids were administered to the patient. After emergence from anesthesia, the patient was awake, alert, and responsive. The LMA was removed, and the patient was moved to the Postanesthesia Care Unit (PACU). In the PACU, the patient’s mental status and hemodynamics were continuously assessed over a period of 35 - 40 minutes. During this time, his clonus gradually resolved and no sedatives or 5-HT antagonists were required. Intravenous ketorolac was administered in the PACU, but he did not receive any additional opioid analgesics.

On further discussion of these symptoms with the patient’s parents, they reported that approximately 6 months earlier the patient had experienced involuntary “tremors and muscle contractions” of his lower extremities. These tremors had occurred at home after taking oral opioid analgesics for a previous knee surgery. They had been accompanied by agitation and mental status changes. His symptoms gradually abated, and the family never sought medical treatment. The patient and his family were informed that the symptoms he experienced at home were likely also a manifestation of serotonin syndrome. The interaction of proserotonegergic agents with certain opioids was discussed in detail with the family. Since he continued to be treated with fluoxetine, they were instructed to seek immediate medical assistance if similar symptoms recurred.

3. Discussion

Proserotonergic agents are used increasingly in clinical practice. The ability to quantify the true incidence of serotonin syndrome associated with their use is limited since many physicians are unfamiliar with its diagnosis. Up to 16% of patients who overdose on proserotonegergic drugs will exhibit signs consistent with serotonin syndrome [2]. The incidence of serotonin syndrome with therapeutic doses is much lower and ranges from 0.2% - 0.5% of patients treated with proserotoninergic agents [3].

Lower extremity clonus was detected shortly after induction of general anesthesia and probably would not have been recognized in a patient receiving neuromuscular blocking agents. Indeed, the patient’s movement was initially attributed to “inadequate anesthesia;” for this reason, the patient’s eyes were untaped to further assess anesthetic depth. At this time, the patient also had nystagmus and diaphoresis. Altman and Jahangiri similarly presented a case of serotonin syndrome that manifested initially as extremity clonus and nystagmus [4]. In their patient, however, the diagnosis was apparent only after reversal of neuromuscular blockade. Common manifestations of serotonin syndrome may go unrecognized in the presence of neuromuscular blocking agents.

Other potential causes of this patient’s lower extremity movement include propofol-induced movement disorder, opioid rigidity, and local anesthetic toxicity. Malignant hyperthermia and neuroleptic malignant syndrome also were considered; however, the patient had not been given any dopamine antagonists and he was receiving a nontriggering anesthetic. There were no trace amounts of volatile agent in the anesthesia circuit since it was a dedicated machine for TIVA. Although we considered alternative diagnoses, none could explain the simultaneous occurrence of nystagmus, diaphoresis, and clonus.

This patient’s clonus and nystagmus were most obvious after his initial dose of fentanyl. These findings became gradually more subtle as surgery proceeded. Our decision to continue with the planned procedure was based largely on the continued improvement of the patient’s condition. Other clinicians might justifiably criticize the decision to proceed with an elective surgery under these circumstances.

Patients with serotonin syndrome may experience symptoms ranging in severity from the barely detectable to the overtly life threatening. The diagnosis is made by identifying clinical signs of serotonin toxicity such as autonomic dysfunction, mental status changes, and neuromuscular disorders [5]. A number of different criteria must be present to diagnose serotonin syndrome; however, the most consistent clinical sign is clonus [6]. This patient exhibited ocular and lower extremity clonus as well as diaphoresis. In contrast to the relatively mild symptoms noted in this case, severe serotonin syndrome also may cause autonomic instability (severe hypertension and tachycardia), metabolic acidosis, rhabdomyolysis, renal failure, disseminated intravascular coagulopathy, and hyperthermia that may become life threatening [7].

A number of different medications have been implicated in causing serotonin syndrome. We refer the reader to the excellent reviews that contain comprehensive lists of these drugs [4,5,7]. Of all the agents associated with serotonin
syndrome, opioids are especially notable for the anesthesiologist. Phenylpiperidines (fentanyl, in particular) have been linked anecdotally to serotonin syndrome [8-10]. Gilman et al showed that phenylpiperidines were weak SSRI’s [11]. For this patient’s anesthetic, fentanyl and its congener remifentanil were major components. Fig. 1 is a pharmacokinetic simulation (Applied Medical Visualizations, Salt Lake City, UT, USA) of fentanyl-equivalent (combined effect of remifentanil and fentanyl) effect-site concentrations \( (C_e) \) over time.

Thus, when the remifentanil infusion was discontinued, \( C_e \) had decreased to 1 ng/mL. Other reports of perioperative serotonin syndrome have also listed fentanyl as a causative agent [4]. There have also been several reports of serotonin syndrome associated with the use of methylene blue and proserotonergic agents. The proposed mechanism is inhibition of the monoamine oxidase A (MAO-A) enzyme [12].

The treatment of serotonin syndrome begins with removing any precipitating drugs. In this case, the patient had received a single dose of fentanyl at the beginning of the case, and subsequently received remifentanil by infusion. Thus, when the remifentanil infusion was discontinued, \( C_e \) decreased rapidly to <1 ng/mL and the patient did not require any further intervention. Fortunately, this patient’s postoperative analgesia was adequately managed with local anesthetic through an indwelling femoral nerve catheter. No further IV opioids were necessary.

Supportive therapy often is all that is needed after removing the offending agent. Most cases of serotonin syndrome improve or resolve within 24 hours after cessation of the precipitating drugs. Several pharmacotherapies for the treatment of serotonin syndrome are described. Among the most relevant, administration of 5-HT antagonists, primarily cyproheptadine, may rapidly resolve central nervous system symptoms [5]. Benzodiazepines also have been used to treat agitation that is often present [7]. In cases of severe serotonin syndrome, intensive care unit admission, tracheal intubation, sedation, and neuromuscular block may be required.

4. Conclusion

As the use of proserotonergic medications continues to increase, the incidence of serotonin syndrome is also likely to increase [13]. It is important to recognize the unique presentations of this syndrome in the perioperative setting. Since opioid analgesics, particularly phenylpiperidines, are known to precipitate serotonin syndrome [8-10], special consideration should be given to their use in patients treated with proserotonergic agents. Patients treated with a proserotonergic agent should be questioned specifically during the preoperative evaluation about any history consistent with serotonin syndrome. Those with a prior history suggestive of serotonin syndrome are best managed by avoiding phenylpiperidines in favor of alternative analogues. Finally, serotonin syndrome might initially manifest during general anesthesia as clonus that may not be detected in the presence of neuromuscular blockade.

References
