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■ Case Report ■

Probable tramadol-induced atypical serotonin syndrome in a patient receiving selective serotonin reuptake inhibitor and stopped at 10 days before surgery -A case report-

Department of Anesthesiology and Pain Medicine, Myongji Hospital, Goyang, Korea

Yoo Kang, Jinhye Min, Young Keun Chae, Sang-eun Lee, Ui-jin Je, and **Yong Kyung Lee**

Tramadol can increase the serum level of serotonin, causing serotonin syndrome, which is a potentially life-threatening condition. Serotonin syndrome occurs when tramadol is used in combination with other drugs that affect serotonin. A patient who had been taking selective serotonin reuptake inhibitor and stopped at 10 days before surgery experienced intermittent heart rate elevation, tremor of the upper extremities and mental change after receiving an infusion of tramadol for postoperative pain control. Although he did not show the typical triad of serotonin syndrome (systemic autonomic dysfunction, neuromuscular impairment and mental status change), the patient was suspected to have serotonin syndrome caused by tramadol. **(Anesth Pain Med 2014; 9: 115-118)**

Key Words: Postoperative pain control, Selective serotonin reuptake inhibitors, Serotonin syndrome, Tramadol.

Among different postoperative analgesics, tramadol is widely used as it produces the effect of opioid analgesia without producing side effects such as respiratory failure. Its mechanism of action is similar to morphine, which works through activation of opioid mu-receptors. Additionally, it blocks reuptake of both serotonin and norepinephrine in the central nervous system, which in turn inhibits ascending pain pathways [1]. There are two types of side effects of tramadol: those that relate to its action on opioid receptors (nausea, vomiting, drowsiness, constipation, urinary retention, etc.), and those that relate to the inhibition of serotonin and norepinephrine reuptake (headache, dizziness, cold sweating, dry mouth, etc.). The most feared sides effect is seizure, which is more likely to occur when tramadol is administered in combination to drugs influencing serotonin pathways [2]. Serotonin syndrome as a complication of tramadol use is rare but may be fatal if it occurs. It is more likely to occur when drugs that influence the uptake or production of serotonin are given concomitantly with tramadol. Typical symptoms of serotonin syndrome include systemic autonomic dysfunction, neuromuscular impairment, and mental status change. This potential complication is hard to diagnose because it can only be diagnosed after excluding other causes, and a delay in diagnosis can lead to the failure of timely treatment [3]. Since serotonin syndrome rarely occurs, this syndrome will be discussed in a literature review.

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Corresponding author: Yong Kyung Lee, M.D., Department of Anesthesiology and Pain Medicine, Myongji Hospital, 697-24, Hwajeong-dong, Deogyang-gu, Goyang 412-270, Korea. Tel: 82-31-810-6205, Fax: 82-31-810-6203, E-mail: mdtweety@kd.ac.kr

CASE REPORT

A 62-year-old male patient (165 cm, 66 kg) with an incidentally found solitary pulmonary nodule underwent a needle aspiration biopsy, which revealed the lesion to be adenocarcinoma. The patient was admitted to our institution for a video-assisted thoracoscopic left lower lobectomy. The patient had a medical history significant for traumatic intracranial hemorrhage 10 years ago, for which he was taking escitalopram, a selective serotonin reuptake inhibitor (SSRI). Additionally, the patient was taking buspirone, quetapine, and clonazepam for anxiety, sleep disorder and intermittent upper limb tremor, respectively. He was also on medications for hypertension and benign prostatic hypertrophy. All his medicines, including escitalopram, had been stopped 10 days before surgery.

In the preoperative evaluation, the result of chest X-ray revealed no changes to the nodule in the left lower lobe, and

other preoperative evaluations were expected normal findings, including the arterial blood gas analysis (pH 7.41, pCO_2 38 mmHg, pO_2 106 mmHg, HCO^- 24 mEq), electrocardiography and laboratory blood tests. In addition, positron emission tomography - computed tomography and brain magnetic resonance imaging did not identify any metastatic lesions.

Upon arrival at the operating room, non-invasive monitoring of the blood pressure, pulse oximetry, and bispectral index score monitoring (BIS), which estimated the depth of anesthesia, were begun. Remifentanil was consistently infused at 200 μg/h, and propofol 2 mg/kg and rocuronium 0.8 mg/kg were given intravenously for induction, and then the patient was intubated with a double-lumen endotracheal tube (37 fr.). After intubation, a 20-gauge angio-needle was inserted into the right radial artery for invasive arterial blood pressure monitoring, and a central venous catheter was inserted into the right internal jugular vein. Through the induction phase of anesthesia, the vital signs remained stable, and both sevoflurane and remifentanil were used to maintain anesthesia, while rocuronium 15 mg was injected every hour. After 25 minutes into the operation, the blood pressure had dropped to 88/43 mmHg, but responded to 107/56 mmHg after an infusion of phenylephrine 80 μg and ephedrine 10 mg. Through the remainder of the operation, the systolic blood pressure was maintained at 98–125 mmHg, heart rate at 60–80 beats/min, oxygen saturation as 96–100%, and BIS maintained between 40 and 60. Total operation time was 2 hours and 55 minutes, and total anesthesia time was 3 hours and 45 minutes. Estimated blood loss was not high, and no transfusion was given. Normal saline 950 ml and colloid 800 ml were given intravenously. The urine output was 0.4 ml/kg/h, which was suspected to be oliguria, but diuretics were not used because urine output had increased to 1.3 ml/kg/h soon after the surgery. The patient recovered spontaneous respiration without any problems, and oxygen saturation was well maintained. Both pyridostigmine 15 mg and glycopyrrolate 0.4 mg were given intravenously for complete antagonism of muscle relaxation, and the patient recovered full consciousness.

After the surgery, patient control analgesia (PCA) was initiated, which consisted of fentanyl 1000 μg and ketorolac 120 mg (the basal infusion rate for fentanyl was 0.3 μg/kg/h with an additional 0.15 μg/kg bolus every 10 minutes as patient wished). For additional pain control, tramadol was used every time the patient complained of pain, and tramadol 100 mg was given intramuscularly after the surgery. Six hours after the surgery, a mixture of tramadol 100 mg and normal saline 100 ml was infused intravenously for 30 minutes at patient request. After the intravenous infusion of tramadol, the patient complained of headache and nausea, but the symptoms improved after a while, and no other accompanying symptoms or sequelae appeared. On postoperative 1 day at 5 : 30 in the morning, he complained of operative site pain, and the patient was again given a mixture of tramadol 100 mg and normal saline 100 ml over 10 minutes. Two hours later during observation in the intensive care unit, the patient showed decreased alertness and did not respond to stimuli. A full neurological exam revealed normal cranial nerve reflexes and deep tendon reflexes, although there was no response to painful stimuli. He did not make voluntary body movements, but when his knee was raised, the leg maintained the position. The pulse temporarily increased to over 100 beats/min, but there was no change in blood pressure, oxygen saturation, or facial expression. The results of the blood test were all in the normal range (Table 1), and brain imaging revealed nothing unusual. During this time, the patient continued to be in a lower state of consciousness, with eyeball deviation and tremors in the upper extremities that lasted for 1 to 2 minutes and eventually stopped, but with adequate oxygen saturation. Thus, it was hard to consider the tremors as the tonic-clonic and generalized type of seizure, which would be expected for tramadol-induced seizure [4]. Six hours after the infusion of tramadol, the patient recovered consciousness during the placement of a nasogastric tube for enteral administration of medications, and both sensory and voluntary neurologic functions returned to normal. According to the patient after regaining consciousness, he had felt nausea and dizziness during the infusion of tramadol and later lost the sense of pain, but still maintained normal hearing and vision and could feel his limb movements

Table 1. Laboratory Finding

	Result
ABGA	
pH	7.43
PCO_2 (mmHg)	37
PO_2 (mmHg)	82
O_2 saturation (%)	96
CBC	
Hb (g/dl)/Hct (%)/Plt (10^3/μl)	8.8/26/222
Electrolyte	
Na/K/Cl (mM)	142/3.4/109

ABGA: arterial blood gas analysis, CBC: complete blood count, Hb: hemoglobin, Hct: hematocrit, Plt: platelet.

during neurological examination. His neurological condition remained normal, until tramadol was again administered to the patient. At this point, the patient reported symptoms similar to those of the previous episode (nausea and dizziness). Thus, the infusion was immediately stopped. Eight days after the surgery, the patient was discharged from hospital.

DISCUSSION

As mentioned earlier, serotonin syndrome is a potentially fatal side effect of tramadol. Although the presentation was not typical in the patient, it was safer to diagnose him as having serotonin syndrome, based on Hunter's criteria [4]. There are three potential contributing factors [5] of serotonin toxicity in the case: one, the fact that tramadol, which inhibits the serotonin reuptake, was used; two, the patient's long-term use of escitalopram, a SSRI; and three, the constant use of PCA, which has an opioid that increases the secretion of serotonin. In addition, there were symptoms including suspected clonus and tremors as well as eyeball deviation. Although symptoms did not satisfy the triad of serotonin syndrome, the temporary tremors and tachycardia were considered as symptoms of autonomic hyperactivity. Moreover, the patient had taken hypertension drug and antiepileptic agent, clonazepam, for a long time and was used opioid continuously through PCA. Because of this, other symptoms of autonomic hyperactivity might have been masked, and the neurologic symptoms of serotonin syndrome may not have appeared in the typical form.

Based on the Glasgow Coma Scale score, the patient's symptoms showed that he was in a state of coma with 3 points (motor 1 point, eye 1 point and verbal 1 point). The author suspected a locked-in syndrome at first, as quadriplegia and mutism. The term "locked-in syndrome", coined by Plum and Posner in 1966, is a neurological disorder associated with infarction of the ventral pons. Patients with locked-in syndrome are able to communicate through eye movements and blinking [6]. However, the patient in this case report was not able to communicate in any way and was unable even to voluntarily move his facial muscles even while motor tone was still normal, as shown by his leg maintaining the position when the knee was raised. In addition, there were no neurological symptoms later. Thus, the patient was unlikely to have had a locked-in syndrome. Syringomyelia was ruled out because there was no tumor or hemorrhage that produces damage to spinal cord, although such loss of pain sensory with normal touch and joint-position sensations is observed in syringomyelia [7].

The cause of the neurological abnormalities is not clear, but the symptoms did occur after the administration of tramadol and had resolved after approximately six hours, which is approximately the duration of tramadol effects. Moreover, the symptoms have not reappeared since the tramadol was ceased. The result of the blood test and brain imaging showed no abnormal findings, and there were no neurological sequelae. After the first episode, the patient recalled that the initial episode of neurologic symptoms began with dizziness and nausea during the tramadol infusion, followed by diminishing sense of touch and motor function. Later when tramadol was administered again, these prodromal symptoms returned. Thus, the author suspected that the symptoms of patient caused by serotonin syndrome in side effects of tramadol. As such, a diagnosis of serotonin syndrome was made from clinical presentation, even if serum serotonin or tramadol level was not evaluated.

In general, serotonin syndrome commonly occurs when SSRI and tramadol are administrated together. However, the patient in case took opioid and tramadol for postoperative pain control, and has stopped taking escitalopram 10 days before the operation. Drug interaction by SSRI was expected to be insignificant after that interval because of low potency of escitalopram and the short half-life of 27 to 32 hours, relatively. Moreover, serotonin syndrome by tramadol was not suspected at first because any symptom suggestive for serotonin syndrome was not present, and only mild dizziness, nausea, and headache quickly subsided during the infusion 100 mg of tramadol by intramuscular and intravenous. When tramadol was used intramuscularly and intravenously earlier, there was no abnormal neurologic symptom except for the prodrome of dizziness and headache. This was probably because when tramadol was given initially, the inhibitory effect on serotonin reuptake was not strong enough to cause the appearance of symptoms, but the effects gradually accumulated with further administration of tramadol and eventually produced the symptoms. Besides, escitalopram is an inhibitor of the CYP2D6, which is a liver enzyme participating in the metabolism of tramadol, and it can make potentiate the actions of tramadol through increasing the concentration of tramadol in the blood [8]. After taking escitalopram for a long time, the effect of escitalopram is prolonged over the administration period [9]; and the activity of CYP2D6 is slightly reduced [10]. Thus, low activity of CYP2D6 can affect drug interaction between tramadol and escitalopram, although escitalopram was stopped for enough time before surgery in consideration of its half-life.

As for the possibility that an overdose of tramadol caused the atypical responses, the analgesic effect of a tramadol infusion with PCA has been reported at blood concentrations of 0.1–0.3 mg/L, depending on the cause and intensity of pain, and when a dosage of tramadol 100 mg is given intravenously, the blood concentration reaches 0.61 mg/L in 15 minutes and 0.41 mg/L in 2 hours [11]. Doses over 300 mg can have the same analgesic effect as opioid analgesics [12], and doses over 400 mg are used for full analgesia for cases of severe pain after surgery [13]. Furthermore, the minimum dosage of tramadol known cause the fatal side effect of seizure is 200 mg. The minimum to cause a coma and respiratory failure is 800 mg, and the minimum fatal dosage for adults with addiction problems is 1000 mg [4]. All things taken together, the total dosage of tramadol given to the patient in this case was not high enough to cause sensory loss, seizure, or coma, nor would the symptoms have been due to anaphylaxis or hypersensitivity to tramadol because the vital signs were stable during the occurrence of symptoms and because there were no external symptoms such as a skin rash. Additionally, the side effects of opioid addiction such as myosis and respiratory failure did not occur.

In conclusion, this case demonstrates that interaction between SSRI and another medication can occur in patients who have stopped taking SSRI before an operation. Therefore, selecting proper analgesic drug for pain control is especially important for such patients. Drugs affecting serotonin before pain control must be stopped before an operation [8], and non-SSRI mediated analgesics, such as non-steroidal anti- inflammatory drugs, must be selected for pain control [14]. Nevertheless, if pain control measures are inadequate and opioids or tramadol are needed, clinicians should be aware that fatal symptom can occur at any time and that enough monitoring and observation is necessary for early detection of the signs and symptoms of serotonin syndrome.

REFERENCES

1. Nossaman VE, Ramadhyani U, Kadowitz PJ, Nossaman BD. Advances in perioperative pain management: use of medications with dual analgesic mechanisms, tramadol and tapentadol. Anesthesiology Clin 2010; 28: 647-66.
2. Ripple MG, Pestaner JP, Levine BS, Smialek JE. Lethal combination of tramadol and multiple drugs affecting serotonin. Am J Forensic Med Pathol 2000; 21: 370-4.
3. Day LT, Jeanmonod RK. Serotonin syndrome in a patient taking lexapro and flexeril. Am J Emerg Med 2008; 26: 1069.
4. Marechal C, Honorat R, Claudet I. Serotonin syndrome induced by tramadol intoxication in an 8-month-old infant. Pediatr Neurol 2011; 44: 72-4.
5. Gollapudy S, Kumar V, Dhamee MS. A case of serotonin syndrome precipitated by fentanyl and ondansetron in a patient receiving paroxetine, duloxetine, and bupropion. J Clin Anesth 2012; 24: 251-2.
6. Patterson JR, Grabois M. Locked-in syndrome: a review of 139 cases. Stroke 1986; 17: 758-64.
7. Bradley WG, Daroff RB, Fenichel G, Jankovic J. Neurology in clinical practice. 5th ed. Philadelphia, Elservier Inc. 2008, pp 401-12.
8. Nelson EM, Philbrick AM. Avoiding serotonin syndrome: the nature of the interaction between tramadol and selective serotonin reuptake inhibitors. Ann Pharmacother 2012; 46: 1712-6.
9. Kirino E. Escitalopram for the management of major depressive disorder: a review of its efficacy, safety, and patient acceptability. Patient Prefer Adherence 2012; 6: 853-61.
10. Hiemke C, Hartter S. Pharmacokinetics of selective serotonin reuptake inhibitors. Pharmacology & Therapeutics 2000; 85: 11-28.
11. Lehmann KA, Kratzenberg U, Schroeder-Bark B, Horrichs-Haermeyer G. Postoperative patient-controlled analgesia with tramadol: analgesic efficiency and minimum effective concentrations. Clin J Pain 1990; 6: 212-20.
12. Duthie DJ. Remifentanil and tramadol. Br J Anaesth 1998; 81: 51-7.
13. Wiebalck A, Tryba M, Hoell T, Strumpf M, Kulka P, Zenz M. Efficacy and safety of tramadol and morphine in patients with extremely severe postoperative pain. Acute Pain 2000; 3: 1-7.
14. Uher R, Carver S, Power RA, Mors O, Maier W, Rietschel M, et al. Non-steroidal anti-inflammatory drugs and efficacy of antidepressants in major depressive disorder. Psychol Med 2012; 42: 2027-35.