

Seizure developed after palonosetron intravenous injection during recovery from general anesthesia

-A case report-

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Seizure associated with antiemetics is rare. We report seizure associated with a 5-HT₃ receptor antagonist in a 38 years old female. The patient underwent ureterorenoscopic lithotripsy due to left upper ureter stone. After operation, the patient complained of nausea in the postanesthetic recovery unit. In order to subside symptom, the patient was administrated 5-HT₃ receptor antagonist, palonosetron, 0.075 mg intravenously. Shortly after administration of that, the patient developed generalized tonic-clonic seizures. The symptom was subsided after midazolam and thiopental sodium were injected. But 40 minutes later, seizure recurred and subsided with midazolam again. The patient recovered completely without any specific sequelae. (Korean J Anesthesiol 2012; 63: 173-176)

Key Words: Palonosetron, Seizure, 5-HT₃R antagonist.

Various postoperative complications may occur due to many factors such as the general state of the patient, operated region, surgical procedure, administered drug, and genetic factors. Among the various postoperative complications, postoperative nausea and vomiting are the most common complications and they account for a considerable part of the quality of a patient's recovery. For this reason, antiemetics are used to prevent and treat postoperative nausea and vomiting. 5-Hydroxytryptamine type 3 receptor (5-HT₃R) antagonist is commonly used since it is known to have an excellent effect and causes fewer complications than that of other antiemetics. The

rare side effects of 5-HT₃R antagonist include headache, fatigue, sedation, and constipation [1-4]. In a few cases, seizure has occurred after the injection of 5-HT₃R antagonist, which was reported to be suspected as the cause of the seizure [4-6]. Here, we experienced a seizure that developed after the injection of palonosetron, a second-generation 5-HT₃R antagonist, into a patient who had undergone an operation under general anesthesia for the treatment of postoperative nausea and vomiting and thus, report the case with a review of the relevant literature.

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Case Report

A female patient, who was 38 years old, 158 cm tall and weighed 62 kg, underwent ureterorenoscopic lithotripsy for the left upper ureter stone. There was no specific familial medical history, past medical history, or administered drugs. All the results of the preoperative laboratory tests done after the hospitalization including electrocardiogram, chest x-ray, blood examination, and urine examination were in the normal range.

Glycopyrrolate 0.4 mg was intramuscularly injected as the preoperative treatment. After arriving at the operation room, the vital signs including blood pressure, electrocardiogram, oxygen saturation, heart rate, and respiratory rate were stable. Thiopental sodium 300 mg was intravenously injected for induction and rocuronium 35 mg after the loss consciousness. Following the injection, ventilation was performed with 100% oxygen and sevoflurane 3 vol% until the vocal cords were fully relaxed. Intubation was performed after the vocal cords were relaxed fully. While maintaining anesthesia, ventilation was controlled so that the end tidal carbon dioxide tension could be kept at 30–35 mmHg. A concentration of 2–3 vol% sevoflurane was controlled in the inhalation gas along with 50% oxygen and 50% N₂O in order to maintain the depth of the anesthesia appropriate to the operation. The operation took about 25 minutes. Under the ureteroscopy, the ureter stones were crushed and then eliminated. Four liters of normal saline solution was used as the irrigation solution. At the end of the operation, pyridostigmine 15 mg and glycopyrrolate 0.4 mg were intravenously injected after spontaneous breathing was recovered for complete recovery from the muscle relaxant. Extubation was performed after consciousness was recovered. The patient was transferred to the recovery room after the patient's spontaneous breathing and vital signs were stabilized.

When the patient arrived at the recovery room, the vital signs were stable. Using a venturi mask, oxygen 5 L/min was supplied at a inspired oxygen fraction 0.4. After ten minutes, the oxygen supply through the venture mask was stopped and oxygen saturation was continuously kept at 100% on the pulse oximetry. Twenty minutes after arriving at the recovery room, the patient complained of nausea, and thus, palonosetron 0.075 mg was intravenously injected. Seventeen minutes after the palonosetron injection, the patient felt the onset of a bowel movement. While attempting defecation with a bedpan in bed in the recovery room, the patient showed a sudden involuntary movement of four limbs. At the time of the moment when the symptoms were found, midazolam 2 mg and thiopental sodium 50 mg intravenously injected one by one, and oxygen 5 L/min was supplied using a venturi mask. Whether there was loss of consciousness during the involuntary movement was not clear and whether there was eyeball deviation was not verified. The

patient trembled while stretching her four limbs, showing the pattern of a generalized tonic-clonic seizure. There was not salivation, urination, and tongue bite. At that time, the systolic pressure was 125 mmHg, diastolic pressure 80 mmHg, and heart rate 72/min, showing no abnormal findings in the blood pressure, heart rate, and electrocardiography. The involuntary movement disappeared after the injection of midazolam and thiopental sodium. Forty minutes after the symptoms, the patient's consciousness became clear, and her vital signs were stabilized. Thus, recovery room monitoring was finished. A brief neurological examination performed at that time did not show any abnormal findings. While waiting for radiography immediately after being discharged, the patient showed the same pattern of involuntary movement and consciousness was temporarily lost. The patient was immediately transferred to the recovery room where midazolam 2 mg was intravenously injected and oxygen 5 L/min was supplied using a venturi mask again. An arterial blood gas analysis and electrolyte test were performed and the results showed a pH 7.40, PaO₂ 156 mmHg, PaCO₂ 39 mmHg, sodium 143 mEq/L, potassium 3.7 mEq/L, and chloride 106 mEq/L. The body temperature was 36.4°C and the blood sugar level was 81 mg/dl. After the injection of midazolam, the symptoms disappeared and did not recurrence. Since the patient's consciousness recovered and her vital signs were stabilized, she was transferred to the ward one hour after returning to the recovery room.

The symptoms did not reoccur during her hospitalization and the postoperative test did not show any abnormal findings. Thus, the patient was discharged two days after the operation. The postoperative follow-up for six months showed that the seizure had not reoccurred.

Discussion

Currently, various drugs including 5-HT₃R antagonist, dopamine antagonist, corticosteroid, histamine antagonist, anticholinergics, and neurokinin receptor antagonist are used to prevent and treat nausea and vomiting based on different mechanisms. Among them, 5-HT₃R antagonist prevents nausea and vomiting by selectively blocking 5-HT₃R at the gastrointestinal vagus afferent nerve, the chemical receptor in the brain stem, and the solitary nucleus [1,2]. Ondansetron, granisetron, ramosetron, and palonosetron are the representative 5-HT₃R antagonistic drugs. Different from other antiemetics, they have no side effects such as sedation or extrapyramidal symptom, having less generalized action and showing an excellent effect as an antiemetic, and thus, they are most frequently used in recent times [1-3].

Since the side effects by the administration of 5-HT₃R antagonist are relatively rare or mild in general, being temporary

and moderate, it is known that there is almost no case where the administration of the drug has to be stopped [1]. The most common side effect is headache, mild to moderate, which is treated with nonopioid analgesics. Additionally, constipation may occur due to a side effect in the gastrointestinal system, and the hepatic enzyme level may be increased. An electrocardiographic change such as an increased QT interval may be observed, which is clinically insignificant, and the correlation of the change with the 5-HT₃R antagonist is not clear [1,2].

There are a few cases, like our case, where a seizure occurred after the injection of 5-HT₃R antagonist. An accurate mechanism has not been clarified yet but 5-HT₃R antagonist is considered as the cause because other factors of seizure have been excluded in these patients [4-6]. Singh et al. [5] reviewed the medical records of 1,521 patients who underwent ondansetron injection for nausea and vomiting. They found that generalized tonic-clonic seizure lasting 1 minute or less, occurred in three patients among them within 12–22 minutes after the intravenous injection of ondansetron 4 mg. these patients showed normal findings in all the tests except only one showed mild hypokalemia. The electroencephalography and MRI test that were performed later also showed normal findings. No patients showed any signs for recurrence of the seizure for more than six months in the absence of antiepileptic drugs. In other words, the patients who showed seizure did not have any inducers of seizure. Considering the temporal relationship between the injection of ondansetron and the occurrence of the seizure, which is that the seizure occurred at the time when the injected ondansetron might have reached a significant concentration at the central nervous system, ondansetron, which is one type of 5-HT₃R antagonist, is suspected as the cause of the seizure. Recently, Zambelli et al. [4] reported a case of a patient to whom palonosetron 0.25 mg was injected for prevention of chemotherapy induced nausea and vomiting. One hour after the palonosetron injection, a generalized tonic-clonic seizure that lasted for eight minutes occurred and was treated with diazepam. In this case also, there was no other finding that could be suspected as the cause for the seizure except palonosetron. In our case also, there were no other factors that could be suspected as the cause for the seizure in the past medical history including the family medical history as well as in the test results. Although a definitive diagnosis of a seizure could not be made by electroencephalogram or MRI imaging immediately after the occurrence of the seizure, the patient showed a pattern for generalized tonic-clonic seizure as in the previous cases. The patient was sedated by midazolam injection. In the occurrence of the second seizure, the loss of consciousness was certain. After that, the patient recovered without any complications or recurrence.

Epilepsy is a heterogeneous disease group caused by

various factors. Epilepsy, which secondarily occurs by abnormal synchronous discharges of the nervous system network, is triggered by abnormal ionic conduction, changes in neuronal membranes, and an imbalance between excitatory and inhibitory influences. It was shown that 5-HT neurotransmission is involved in the control of seizure induced in various types of experiments. In general, drugs that increase the extracellular 5-HT level repress a seizure and the depletion of cerebral 5-HT increases the sensitivity to convulsions. Among the various subtypes of 5-HT₃R, at least 5-HT_{1A}R, 5-HT_{2C}R, 5-HT₃R and 5-HT₇R are known to be associated with epilepsy [7].

Therefore, it is assumed that 5-HT₃R antagonists may have a direct or indirect effect on the process involved in seizure, and 5-HT₃R antagonists including ondansetron may be considered as proconvulsants or anticonvulsants of convulsion [5]. Although 5-HT₃R antagonists selectively act on the 5-HT₃R, the possibility still remains that they may act on other 5-HT₃R receptors such as 5-HT₁, 5-HT₂, and 5-HT₄ receptors as well as μ -opioid, α -adrenergic, γ -aminobutyric acid (GABA), and glycine receptors that belong to the same ligand gated ion channel [8]. Ye et al. [9] assumed that the clinical occurrence of a seizure due to ondansetron may be caused by the inhibition of the GABA and glycine receptor activity. Grant et al. [10] also reported that MDL 72222, a 5-HT₃R antagonist, exacerbated ethanol withdrawal seizure.

On the contrary, Wada et al. [11] reported that phenyl-biguanide, a 5-HT₃R agonist, extended the duration of seizures in amygdala kindling occurs. Many animal experiments [11,12] have also shown that the occurrence of seizure was repressed by 5-HT₃R antagonists such as zacopride, granisetron and ondansetron. Moreover, considering the fact that the seizures developed after a 5-HT₃R antagonist injection occurred following a normal dose of it including our case and they actually occurred in extremely rare cases, further study and investigation may be required on the role of 5-HT₃R in seizures and on its mechanism. However, in all the seizure cases described above, the 5-HT₃R antagonist was injected when the patients were conscious. Since 5-HT₃R antagonist injection is mostly performed during anesthesia in order to prevent postoperative nausea and vomiting, the occurrence of seizures might have been hid or repressed by general anesthesia or muscular relaxation, and thereby, the occurrence rate might have been underestimated.

On the other hand, palonosetron, a new, second generation 5-HT₃R antagonist based on the fused tricyclic ring to which a part of quinuclidine is attached, induces its effect by blocking serotonin binding, causing a structural change in the receptor, different from the first generation 5-HT₃R antagonists such as ondansetron and granisetron that act as competitive repressors to 5-HT₃R, having a similar structure to that of the 5-HT₃R [13].

Palonosetron is known to act more selectively since it has a high affinity to 5-HT₃R and has a half-life as long as 40 hours [4,14]. Thus, in comparison to the first generation 5-HT₃R antagonists such as ondansetron, palonosetron may have less risk of causing an seizure by not acting on other receptors that are related to the seizure process except for 5-HT₃R. However, considering the seizure in our case in which the patient had been subsided by the injection of midazolam and recurrence after 40 minutes, seizure may last longer once it occurs and it may require longer hours of monitoring since its effective time is longer.

In conclusion, 5-HT₃R antagonists are commonly used in clinics since they are effective in the prevention and treatment of postoperative nausea and vomiting and rarely show complications. Although rare, there is a risk of seizure by the administration of 5-HT₃R antagonists. Even though seizure seems to be a temporary benign complication, it may cause a severe problem in some patients including cardiopulmonary compromised patients. Therefore, care should be taken when injecting a 5-HT₃R antagonist, especially when injecting into a conscious patient. Further studies may need to be done on the incidence rate of seizure developed after 5-HT₃R antagonist injection and on its mechanism.

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