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New Onset Generalized Tonic Clonic Seizures after Intravenous Tramadol with Ondansetron

Jyotirmay Kirtania[1*] and Shreyasi Ray[2]

[1]Department of Anesthesiology, ESI-PGIMSR and Medical College Joka, Kolkata, India.
[2]Department of Anesthesiology, Medical College Kolkata, India.

Authors' contributions

This work was carried out in collaboration between both authors. Author JK provided anesthesia care for the patient, compiled the clinical data for the case report, and wrote the draft of the manuscript. Author SR managed the literature searches and edited the draft manuscript. Both authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: Tramadol hydrochloride is a centrally acting opioid analgesic. Ondansetron is a selective serotonin receptor (5-HT_3) antagonist, primarily used for prevention and treatment of drug-induced and postoperative nausea and vomiting. Tramadol and ondansetron have reported good safety profile in the recommended doses. These two drugs are commonly co-administered. This study aims to highlight a rare but severe adverse effect of co-administration of intravenous tramadol with ondansetron.

Presentation of the Case: A 42-year-old female without prior history of seizure disorder or chronic drug use or acute metabolic or electrolyte disturbances, received tramadol 100 mg with ondansetron 8 mg intravenously before general anesthesia. Within six minutes of the injections, she developed generalized tonic clonic seizures. Seizures were immediately terminated with propofol 50 mg, followed by mask ventilation, tracheal intubation and controlled ventilation. She had an uneventful recovery from surgery under general anesthesia and was later discharged home in a favorable

**Corresponding author: E-mail: jyoti.kirtania@rediffmail.com;*

condition. Postoperative MRI brain and EEG were normal.
Discussion: Tramadol is known to precipitate seizures at higher than recommended doses. Patients with prior seizure disorders and patients receiving selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics can also have seizures precipitated by tramadol. Our patient received a normal dose of tramadol; neither had she any known risk factors for seizures, nor any prior seizure disorder. She did not receive any drug that adversely interacts with tramadol or ondansetron to precipitate seizure, except the co-administration of normal doses of intravenous tramadol with ondansetron.
Conclusion: We conclude that intravenous tramadol with ondansetron at recommended doses can precipitate seizures even in a patient without underlying seizure disorder.

Keywords: Tramadol; ondansetron; seizures; anesthesia; 5-HT_{2c} receptors; glycine antagonism; GABA antagonism.

1. INTRODUCTION

Tramadol hydrochloride is a centrally acting opioid analgesic with non-selective pure agonist action at μ, δ and κ opioid receptors with a higher affinity for the μ receptor. The inhibition of neuronal reuptake of norepinephrine and enhancement of serotonin release contribute to its analgesic effect as well the adverse effects like serotonin syndrome and seizures. [1] Ondansetron is a selective serotonin 5-HT_3 receptor antagonist used for the prevention and treatment of drug-induced and postoperative nausea and vomiting. The 5-HT_3 receptors are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the brain. It is not certain whether its antiemetic action is mediated centrally, peripherally, or in both sites. [2]

2. PRESENTATION OF CASE

A 42-year-old, 64 kg female with acute appendicitis was posted for emergency appendectomy under general anesthesia. Her immediate preoperative status was unremarkable except mild tachycardia (pulse 94/min) and hypertension (BP 162/90 mmHg in supine position). There was no history of any significant pre-existing illness or use of chronic medications or substance abuse. Laboratory studies were normal except mild neutrophilic leucocytosis. Serum urea, creatinine and electrolytes were normal. Following admission, she had received analgesic diclofenac 75 mg deep intramuscular injection, pantoprazole 40 mg intravenous injection (IVI) for prophylaxis of stress ulcer, ceftriaxone 1 g IVI, and metronidazole 500 mg IVI as empiric antimicrobial therapy.

The patient was already receiving normal saline infusion @ 90 mL/h IVI ever since she was put on fasting about 6 hours back. Upon shifting to the operating table, multi-parameter monitor was attached to the patient and initial values were recorded as pulse 96/min, BP 160/92 mmHg, respiratory rate 22/min, SpO2 100%, and surface temperature 36.7°C. Ondansetron 8 mg and tramadol 100 mg slow IVI (each over one minute) were given consecutively. Approximately six minutes following tramadol injection, (while waiting for the surgeon to finish "scrubbing-in" and enter the operating room), the patient emitted a loud and shrill cry, instantly followed by generalized tonic clonic seizures, tongue bite and loss of consciousness. Intravenous propofol was injected slowly at 0.5 mL/second as soon as convulsion was noticed and stopped as soon as visible convulsive movements ceased, followed by positive pressure mask ventilation, tracheal intubation and subsequent pressure controlled ventilation to maintain normocarbia. It was retrospectively noted that only 50 mg propofol (5 mL over 10 seconds approximately) was used. Vecuronium 3 mg IVI was administered to achieve muscle relaxation. The patient's state of oxygenation, ventilation, circulation and temperature was maintained within the normal range throughout the surgery. The bispectral index (BIS) remained in the deep hypnotic state (less than 40) with 50% nitrous oxide in oxygen without the addition of any other volatile anaesthetic agent. Pupils were bilaterally equal sized, mid-dilated (5 mm approximately) with light reflexes absent. Capillary blood glucose (CBG) was 69 mg/dL, immediately after cessation of seizures. Phenytoin 700 mg in 100 mL normal saline was given as IVI over 30 minutes for prophylaxis against further seizure episodes. The patient also received paracetamol 1 g IVI over 15 minutes as analgesic. Ringer Lactate (RL) solution 500 mL IVI was infused intra-operatively. The surgery lasted for about 40 minutes. At the end of surgery, nitrous oxide was

turned off, and the patient was put on pressure support ventilation (pressure support 10 mbar, trigger 2 L/min) with PEEP (5 mbar). After 5 minutes of turning off nitrous oxide, BIS rapidly rose to more than 90 and spontaneous breathing was adequate with trigger of 5 L/min on pressure support 8 mbar, PEEP 5 mbar. Residual neuromuscular blockade was reversed with neostigmine 2.5 mg plus glycopyrolate 0.5 mg IVI given slowly over 3 minutes.

The patient was extubated in the operating room after confirmation appropriate motor response to simple verbal commands (eye opening and tongue protrusion on verbal command) and ability to do sustained head lift for more than five seconds.

The patient was shifted to PACU for postoperative monitoring and routine postoperative care. Postoperative clinical examination including neurologic evaluation was unremarkable. Postoperatively she received oxygen by facemask @ 4 L/min for 2 hours, RL solution @ 90 mL/h IVI, ondansetron 4 mg IVI SOS for treatment of nausea and vomiting, analgesic paracetamol 1 g IVI 6 hourly, pantoprazole 40 mg IVI once daily for stress-ulcer-prophylaxis, ceftriaxone 1 g IVI twice daily and metronidazole 500 mg IVI thrice daily for empiric antimicrobial therapy. Apart from these routine medications she received anticonvulsant phenytoin 100 mg tablets orally twice daily for three days. She was referred to general medicine physician for further evaluation of the episode of seizure. Immediate postoperative electrolytes, urea, creatinine, LFT, arterial blood gas analysis were normal. The patient did not undergo EEG, MRI brain during the hospital stay due to logistic hindrances. She had an uneventful recovery and was discharged home in favorable condition on the fifth postoperative day. She was referred to a neuro-physician to complete the workup recommended for the first-seizure episode. On her first follow-up visit, the patient reported herself to be well with no further episode of seizure, normal EEG and normal MRI brain.

3. DISCUSSION

Tramadol as analgesic has a good safety profile in the recommended doses (50 – 100 mg initial intravenous dose). It is widely used in hospitals where potent opioids like morphine and fentanyl are scarce or unavailable. Tramadol can increase the risk of seizures in patients on selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure threshold-lowering drugs (e.g. bupropion, mirtazapine, tetrahydrocannabinol). Seizures have also been reported after administration of high dose of tramadol, and in patients with pre-existing seizure disorder [1,3].

Throughout the 12 years of total experience of the first author, and the 8 years of total experience of the second author in clinical anesthesia, this patient is the first one to have had suffered such a seizure after co-administration of tramadol with ondansetron, given the fact she did not have a prior history of seizure disorder or underlying seizure disorder. However, the occurrence of seizures by normal dose of tramadol in patients with underlying seizure disorders (treated or untreated) is well known and has been reported in the literature.

Our patient was non-diabetic and was not on any hypoglycaemic medications or seizure threshold-lowering drugs. CBG immediately after control of the seizure episode was 69 mg/dL. Mild hypoglycaemia (CBG 50 – 70 mg/dL) in fasted non-diabetic adults does not cause seizures, although prolonged and severe hypoglycaemia (CBG < 50 mg/dL for more than 2 hours) can cause seizures and coma [4]. Ceftriaxone, metronidazole, pantoprazole and diclofenac do not have any adverse drug interactions with tramadol or ondansetron [1,2]. Although rare, concomitant use of ondansetron and tramadol can precipitate serotonin syndrome [2]. The salient clinical features of serotonin syndrome include: (1) Autonomic hyperactivity: hypertension, tachycardia, hyperthermia, hyperactive bowel sounds, mydriasis, excessive sweating. (2) Neuromuscular abnormality: tremor, inducible or spontaneous clonus, ocular clonus, hypertonicity, hyperreflexia (this symptom can be masked if there is severe muscle rigidity), and (3) Mental status changes: anxiety, agitation, confusion, coma.

Our patient received 100 mg of tramadol (1.6 mg/kg in our 64 kg patient), which was within the recommended dose range (1 – 2 mg/kg). Also the dose of ondansetron was 8 mg (0.125mg/kg), which was within the recommended dose range (4 – 16 mg) for adults.

Our patient received a normal dose of tramadol and ondansetron; neither had she any known risk factors for seizures, nor any prior seizure

disorder (excluded by clinical history and normal MRI brain and EEG in the postoperative period). She did not receive any drug that adversely interacts with tramadol or ondansetron to precipitate seizure.

Apprehension and anxiety in the immediate preoperative period can cause spontaneous hyperventilation leading to acute respiratory alkalosis. But, generalized seizures are rare unless the alkalosis is severe or the patient has underlying seizure disorder.

The reduction of seizure threshold by tramadol could be attributed to tramadol's putative inhibition of $GABA_A$ receptors at high doses [5]. Our patient received a normal dose of tramadol. So this mechanism of action causing seizure can be ruled out.

In addition, tramadol's major active metabolite, o-desmethyltramadol, is a high-affinity ligand of the δ- and κ-opioid receptors. Activity at the δ-opioid receptor could be involved in tramadol's ability to provoke seizures in susceptible individuals with prior seizure disorder, as δ-opioid receptor agonists are well known to induce seizures [6]. Our patient did not have any history of prior seizure disorder and had normal EEG and MRI brain in the postoperative period. So this mechanism of seizure can be ruled out.

Tramadol has inhibitory actions on the 5-HT_{2C} receptor. 5-HT_{2C} blockade by tramadol may account for its lowering of the seizure threshold, as 5-HT_{2C} knockout mice display significantly increased spontaneous seizures, lowered seizure threshold, enhanced seizure propagation and sound-induced seizure susceptibility [7,8]. Ondansetron can penetrate the blood brain barrier, although slowly [9]. Ondansetron competitively suppresses the chloride currents activated by GABA or glycine in patch-clamped hypothalamic and hippocampal neurons of rats. By preventing the influx of chloride ions, subsequent hyperpolarization is also inhibited by ondansetron. This anti-GABA and anti-glycine property of ondansetron may play a significant role in the ondansetron-potentiated seizures observed in vivo [10]. The inhibition of 5-HT_{2C} receptors by tramadol, coupled with GABA and glycine antagonism by ondansetron in the brain might be the probable mechanism of seizure in our patient.

Such seizures can be masked by relaxant-general-anaesthesia administered immediately after ondansetron and tramadol. In our patient, the time delay of six minutes may have unmasked the seizure. The true incidence of such seizures may be much higher than anticipated and might be underreported.

4. CONCLUSION

We conclude that intravenous tramadol with ondansetron at recommended doses can precipitate seizures even in a patient without an underlying seizure disorder. All patients must be monitored closely with resuscitative measures ready at hand, whenever intravenous tramadol and ondansetron are co-administered.

CONSENT

After listening to a transcript of this case report in native language, the patient gave written consent to the authors to publish this case report.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Tramadol Hydrochloride 50 mg/mL Solution for Injection or Infusion: Summary of Product Characteristics; (12/2012). Available:http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1431666156107.pdf (Accessed:29th July 2015).
2. Ondansetron 2 mg/mL Solution for Injection: Full prescribing information; (09/2014). Available:https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Zofran_Injection/pdf/ZOFRAN-INJECTION.PDF (Accessed: 29th July 2015)
3. Raiger LK, Naithani U, Bhatia S, Chauhan SS. Seizures after intravenous tramadol given as premedication. Indian J Anaesth 2012;56:55–7.
4. Cryer P E. Hypoglycaemia, functional brain failure, and brain death. J Clin Invest. 2007;117:868–70.
5. Hara K, Minami K, Sata T. The effects of tramadol and its metabolite on glycine,

gamma-aminobutyric acid$_A$, and N-methyl-D-aspartate receptors expressed in Xenopus oocytes. Anesth Analg. 2005;100(5):1400-5.

6. Potschka H, Friderichs E, Löscher W. Anticonvulsant and proconvulsant effects of tramadol, its enantiomers and its M1 metabolite in the rat kindling model of epilepsy. Br. J. Pharmacol. 2000;131(2): 203–12.
7. Applegate CD, Tecott LH. Global increases in seizure susceptibility in mice lacking 5-HT$_{2C}$ receptors: a behavioral analysis. Exp Neurol. 1998;154(2):522-30.
8. Heisler LK, Chu HM, Tecott LH. Epilepsy and obesity in serotonin 5-HT$_{2C}$ receptor mutant mice. Ann N Y Acad Sci. 1998;861:74-8.
9. Simpson KH, Murphy P, Colthup PV, Whelan P. Concentration of ondansetron in cerebrospinal fluid following oral dosing in volunteers. Psychopharmacology. 1992;109(4):497-8.
10. Ye JH, Ponnudurai R, Schaefer R. Ondansetron: A selective 5-HT$_3$ receptor antagonist and its applications in CNS-related disorders. CNS Drug Reviews. 2001;7(2):199–213.

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