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Repeated generalized seizures shortly after single intramuscular dose is an additional reasonable cause to restrict the use of ondansetron: A case report

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ABSTRACT

Background: Ondansetron, a 5-hydroxytryptamine (5-HT) receptor antagonist, is generally regarded as a safe and well tolerated antiemetic. Meanwhile, some reports mentioned that it is a probable cause of single generalized seizures after intravenous administration. Our report may be the first to indicate repeated generalized seizures after intramuscular therapeutic dose of ondansetron. Methods and Results: We report a 24-year-old female with nausea and vomiting related to gastritis that experienced repeated ondansetron-induced seizures shortly after a single intramuscular therapeutic dose. Two minutes after intramuscular injection of 4 mg ondansetron, our patient developed the first generalized seizure. Within the following two hours, seizures occurred two more times. In the emergency department, the patient developed a fourth, but weaker and shorter, generalized seizure. The patient was not hypoglycemic, but her blood hemoglobin and serum electrolytes were below normal. A few hours later, the patient was discharged. The dramatic onset of the seizures, as well as the complete recovery and absence of any neurological sequel in our patient, indicated that it was probably related to ondansetron. Conclusion: Patients should be informed about the potential side effects of ondansetron especially the life-threatening repeated generalized seizures, and clinicians should restrict its use to hospitalized patients.

Keywords: Ondansetron; Seizures; 5-Hydroxytryptamine Receptor Antagonist

1. INTRODUCTION

Ondansetron (zofran) a selective 5-hydroxytryptamine (5-HT3) receptor antagonist is frequently used to treat severe nausea and vomiting associated with cancer chemotherapy, radiotherapy, anesthesia, surgery as well as drug over-dosage or poisoning [1].

Case Report

A single dose of 4 mg ondansetron was intramuscularly injected to a 24-year-old female. Two days before administration of ondansetron, she received oral domperidone (motilium) as 5 mg tablets twice daily to control vomiting related to gastritis. The patient had no previous history of seizures, head injury or meningitis. She developed four generalized tonic-clonic seizures; the first one occurred within two minutes after the injection. Within the following two hours, seizures occurred two more times. The time lasting between the first and second seizures was about thirty minutes. The patient's body weight was 60 Kg. The blood pressure and pulse rate were 90/60 mmHg, 60/minute, respectively. In the emergency clinic, the patient developed a fourth, but weaker and shorter, generalized seizure. She received intravenous rehydration therapy in the form of 500 mL of ringer followed by 500 ml of normal saline. Her random blood glucose level was 80 mg/dl as checked by a glucometer. The acid base properties, liver function tests, serum creatinine and blood urea nitrogen were all normal. The total hemoglobin (11.1 g/dL), serum electrolytes (sodium 133 mmol/L, potassium 3 mmol/L and calcium 0.87 mmol/L) were below the reference limits (Sodium: 135 - 145 mmol/L; potassium: 3.5 - 5.1 mmol/L; calcium: 1.12 - 1.32 mmol/L). The patient as well as her parents refused to have further investigations as electroencephalography (EEG), computed tomography or magnetic resonance imaging, as she remained seizure free without antiepileptic drugs.

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2. DISCUSSION

Serotonin 5-HT3 receptors are present in both the central and peripheral nervous systems and are associated with several serotonin-mediated physiological and pathological processes. Ondansetron (a carbazole derivative), is a competitive and selective antagonist of serotonin 5-HT3 receptors. As antiemetics, it decreases vagal activity and inhibits the vomiting center in the medulla oblongata. Also, it decreases the activity of the chemoreceptor trigger zone by blocking the serotonin receptors in the brain. Ondansetron undergoes extensive hepatic oxidative metabolism. Its metabolites contribute little to the activity of the drug and are excreted in the urine and faeces. Renal clearance accounts for less than 5% of total clearance of this drug. Cytochromes P450 IA2, 2D6 and 3A are involved in its hydroxylation. Therefore, in addition to cross-reactivity between ondansetron and agents that compete for these enzymes, toxicity can occur in patients with liver disease [2].

Ondansetron is generally considered as a safer drug than conventional antiemetics. However, many researchers reported a number of potential adverse reactions in relation to this drug. Some of these effects include recurrent bowel occlusion, extrapyramidal manifestations, severe hypoglycemia, hypotension, hypersensitivity reactions as well as acute chorea [1-4]. Thus, Frigerio *et al*. [5] recommended restriction of ondansetron use.

Using the Naranjo adverse drug reaction probability scale [6], some case reports indicated that ondansetron is a probable cause of single generalized seizures that appeared with the intravenous standard dose (as summarized in **Table 1**).

Domperidone (motilium) is a dopamine-antagonist with anti-emetic function for relieve of symptoms of nausea and vomiting. The Netherlands Pharmacovigilance Centre Lareb received some reports of seizures in association with domperidone [10]. Motilium-induced seizures was ruled out due to intake of oral small dose (5 mg), stopping the drug many hours before seizures, as well as absence of seizures with previous intake of the same drug by our patient.

3. CONCLUSION

The current as well as previous reports indicate that ondansetron administration is associated with many adverse reactions including seizures. These seizures are not dose-dependent and may start within less than two minutes. It may be single or repeated and can occur with any route of adminstration. Patients should be informed about these potential side effects. Also, physicians should be more cautious while prescribing this medication to out-patients where prompt treatment may not be possible.

4. BIOETHICAL APPROVAL

This case study was performed in accordance with Declaration of Helsinki and was approved by the Research Ethics Committee of Ain Shams University, Cairo, Egypt. An informed consent was obtained from the patient.

Table 1. Reports indicating occurrence of generalized seizures after intravenous therapeutic dose of ondansetron.

Authors	No. Patients	Age (year)/sex	Dose (Route of adminstration)	Seizures occurrence after ondansetron	Number of seizures	Medical history (Concomitant medications)
Patel *et al*. [1]	1	4/M	0.13 mg/kg (I.V.)	30 minutes	2	Gastroenteritis
Sharma, Raina [3]	1	55/F	4 mg (I.V.)	First (or third) day of chemotherapy cycle	1/each cycle	Metastatic breast cancer (Chemotherapy)
Sargent *et al*. [7]	1	28/M	10 mg (I.V.)	90 minutes	1	Pancreatitis, septic shock, cardiac arrest (methadone, Imipenem)
Mason *et al*. [8]	1	26/F	4 mg (I.V.)	4 minutes	1	Prophylaxis for postoperative nausea & vomiting (Epidural analgesia, oxytocin)
		36/F	4 mg (I.V.)	12 minutes	1	Migraine (Tylenol, Motrin)
Singh *et al*. [9]	3	56/F	4 mg (I.V.)	15 minutes	1	Diabetic ketoacidosis (Insulin, metformin)
		46/M	4 mg (I.V.)	22 minutes	1	Gastritis (Cetirizine)

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