Intraoperative Life-Threatening Cardiac Complication of Ondansetron and its Management: Case Report

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ABSTRACT

Introduction: Ondansetron, 5-Hydroxytryptamine Type 3 (5-HT3) antagonist has been the first-line drug of choice for postoperative nausea and vomiting. There are many side effects common and uncommon reported due to this drug.

Case report: We report a case of intraoperative hypotension, and atrial fibrillation in a female patient who had no prior cardiac history during an elective left ovarian dermoid cyst excision surgery. A literature search was also performed for reports of other cardiovascular events associated with ondansetron.

Conclusion: Ondansetron should be used judiciously and electrolyte parameters should be carefully monitored prior to use till at least 2 hours after intravenous administration of this drug.

Keywords: Life-Threatening, Cardiac Complication, Ondansetron

INTRODUCTION

Ondansetron, 5-Hydroxytryptamine Type 3 (5-HT3) antagonist has been the first-line drug of choice for postoperative nausea and vomiting. Besides its commonly reported side effects like headache in up to 42% of patients, xerostomia (5-17%), diarrhoea (upto 5%), abdominal discomfort some less common effects range from central nervous system (CNS) manifestations of sedation, allergic reaction to serious cardiovascular adverse effects like coronary vasospasm, supraventricular tachycardia, atrial fibrillation, ventricular tachycardia.

We report a case of intraoperative hypotension, and atrial fibrillation in a female patient who had no prior cardiac history during an elective left ovarian dermoid cyst excision surgery. A literature search was also performed for reports of other cardiovascular events associated with ondansetron.

CASE REPORT

A 39 year old female, ASA PS Class I, no history of allergy and unremarkable past medical history was posted for elective left ovarian dermoid cyst excision under regional anaesthesia. Preoperative blood investigations and 12 lead ECG was normal (Figure 1). After attaching routine standard monitors, PR of 78bpm, Blood pressure 126/80. Subarachnoid block was given at L3 L4 interspace with 15mg bupivacaine in dextrose solution and 25mcg of Fentanyl was added as adjuvant, in sitting position for expected 3 hour duration surgery.

T6 Level of sensory block was achieved within 4 minutes. Throughout the surgery, the patient’s vitals were stable. At the end of surgery, when HR was 85 bpm and BP was 130/76 Ondansetron 4mg IV was given to prevent post operative nausea and vomiting (PONV). Immediately after administration of the drug, there was tachycardia up to 160 bpm and followed by hypotension BP 80/50mmHg. Patient was given 700ml fluid bolus. The continuous electrocardiograph monitor revealed irregular narrow complex tachycardia. Clinically patient had excessive sweating, became drowsy but arousable to verbal commands. Patient’s chest, upper limbs were examined for rashes and ruled out anaphylaxis. Hudson mask was put with flow rate at 5 litres/min. Immediately 12 lead ECG was taken and confirmed the presence of atrial fibrillation (figure 2). Blood sugar was within normal levels. Ultrasound abdomen was done to rule out any acute haemorrhage. Transthoracic 2D echo was done, showed normal left ventricle systolic function and no regional wall motion abnormalities Arterial Blood Gas analysis suggested mild metabolic acidosis (pH 7.34), potassium 3.4 mmol/L (normal 3.6 – 5.2 mmol/L) and magnesium 0.39 mmol/L (normal 0.6 – 1.1 mmol/L).

Blood pressure remained low even after boluses of fluid.
Questions | Yes | No | Don’t Know
---|---|---|---
1. Are there previous conclusive reports on this reaction? | +1 | 0 | 0
2. Did the adverse event appear after the suspected drug was administered? | +2 | -1 | 0
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered? | +1 | 0 | 0
4. Did the adverse event reappear when the drug was re-administered? | +2 | -1 | 0
5. Are there alternative causes that could on their own have caused the reaction? | -1 | +2 | 0
6. Did the reaction reappear when a placebo was given? | -1 | +1 | 0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic? | +1 | 0 | 0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased? | +1 | 0 | 0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | +1 | 0 | 0
10. Was the adverse event confirmed by any objective evidence? | +1 | 0 | 0

Table-1:

**Figure-2:** 12 lead ECG showing atrial fibrillation

therefore noradrenaline infusion was started at 0.1 mcg/kg/min. 2 gm of magnesium sulphate was given over 20 minutes with 100 ml of NS. After about 30 mins sinus rhythm started to appear on continuous ECG monitor and heart rate decreased to 120/min. Noradrenaline was gradually tapered down when mean arterial BP is >70 mmHg and was discontinued. After monitoring the vitals within the Operative room for 60 minutes, patient was shifted to post operative room with standard monitoring attached and also blood sample was sent in immediate postop for troponin and electrolytes which came out to be normal. A repeat 12 lead ECG and 2D Echo done by the cardiologist on the next day as follow up was also normal and discharged to home after three days.

**DISCUSSION**

Ondansetron hydrochloride a 5HT antagonist which preferentially bind to the 5-HT3 receptor, FDA approved for the prevention of nausea and vomiting associated with cancer chemotherapy, radiotherapy and postoperative nausea and/or vomiting.¹ Vomiting centre is generally activated by four pathways i.e 1) vagal afferent pathway 2) vestibular system 3) forebrain and 4) area postrema. The afferent vagal fibres, which innervates the stomach and intestine, stimulated by serotonin released from enteroendocrine cells.² Antiemetic effect of Ondansetron involves antagonism of 5-HT3 receptor both peripherally in the gut which is an afferent for Cavallazzi response and centrally in the area postrema which contains the “chemoreceptor trigger zone”.³ Serotonin receptors can be grouped into five main types, namely 5HT1, 5HT2, 5HT3, 5HT4 and 5HT5. They are involved in various physiological functions like thermoregulation, gastrointestinal motility, blood coagulation, and cardiovascular homeostasis. Enterochromaffin cells of the gastrointestinal tract, serotonergic neurons of the CNS and platelets are the major storage site for serotonin.³ Despite its excellent record of safety, serious cardiac side effects such as like coronary vasospasm, supraventricular and ventricular tachycardia and ECG changes like prolonged PR, QRS and QT intervals have also been reported in healthy individuals without any cardiac comorbidities.⁴ ⁵ The first clinical case of ondansetron induced cardiac event noticed in 1992 by Ballard et al in patients undergoing cancer chemotherapy.⁶ Ondansetron blocks the emetogenic impulses by blocking depolarisation of 5HT3 receptors. serotonin secreted in gut mucosa acts on 5HT3 receptors and emetogenic impulses reach CTZ through vagal afferents. Orally, ondansetron has bioavailability about 60 – 70%. Metabolised extensively in the liver mainly hydroxylation by CYP1A2, 2D6. Hepatic elimination is about 95%, <5% is eliminated in the urine unchanged. Half-life of about 3-5 hours and duration of action about 4 -12 hours. Used as first-line drug for nausea and vomiting, prevent vomiting in chemotherapy/radiotherapy patients, prophylaxis for PONV. Effective in 60-80% of cases. Contraindicated in allergic patients. Ondansetron is generally well tolerated, most common side effect is headache in up to 42% cases. Diarrhoea, abdominal discomfort, xerostomia, extrapyramidal symptoms(<1%) are also reported. Serious complications like QTc prolongation, cardiac arrhythmias are associated especially after intravenous administration. Cardiac complications after use of intravenous ondansetron in patients with significant cardiac history/dysfunction, electrolyte abnormalities are reported and must be cautious and irrational use of ondansetron for prophylaxis in patients with electrolyte imbalance and cardiac dysfunction. Development of cardiac adverse events due to ondansetron can be explained by several mechanisms. Firstly Ondansetron primarily blocks HERG potassium channels, the main repolarizing channel in cardiac muscle action potential hence prolonging the QT interval⁷ Drug-induced long QT syndrome is generally asymptomatic until some type of pause in the form of AV block or ectopic beats stimulate it to
produce ventricular arrhythmia and tordes de pointes. Drug-induced long QT converted to more dangerous arrhythmias when associated with other risk factors like rapid infusion by intravenous use, female sex, hypokalemia, hypomagnesemia, hypocalcemia, heart disease and genetic predisposition. Electrolyte abnormalities like hypokalemia, hypocalcemia in the patient reduces repolarisation reserve of the heart, which may be subclinical until drugs blocking HERG potassium channels are given, which leads to drug-induced QT prolongation. Secondly, blockade of 5HT3 receptor lead to vasoconstriction and hypertension by unopposed action of 5HT2 and 5HT4 receptors. Thirdly 5-HT3 receptors located on sensory vagal nerve endings in the heart which cause an initial short-lasting hypotension due to bradycardia via von Bezold-Jarisch like reflex. And blockade of this reflex by 5HT3 antagonist like ondansetron can precipitate tachycardia and hypertension. Fourthly the rate of administration of the drug. Recommendation from the manufacturer is to give 8mg of Ondansetron over 30 seconds but in our case, 4mg ondansetron was given in 5 seconds.

Although the maximal mean QTc interval lengthening was observed at 3 minutes after administration, as the half-life of ondansetron is 5.7 hours, drug within the central compartment may have a potential impact on myocardial tissue after a prolonged period, as shown by the prospective observational study by Hafermann et al who showed QTc prolongation after 120 minutes. Therefore we recommend to monitor patients for at least 2 hours post-administration of ondansetron.

However, we describe a patient with no history of cardiac abnormalities who experienced a severe episode of acute myocardial ischemia that occurred immediately after intravenous injection of ondansetron during intraoperative period. Ondansetron as a cause of development of atrial fibrillation cannot be conclusively established, causality assessment by Naranjo probability scale (Table 1) was six, indicating a probable adverse drug reaction.

**CONCLUSION**

Even though an idiopathic aetiology cannot be ruled but we strongly suspect that ondansetron caused the atrial fibrillation and hypotension in this case, as a nonsignificant past medical history, as well as the timing of administration of other medications, support this conclusion. Further investigation is needed to delineate the clinical safety of ondansetron. Till such time ondansetron should be used judiciously and electrolyte parameters should be carefully monitored prior to use till at least 2 hours after intravenous administration of this drug.

**REFERENCE**

1. ZOFRAN (ondansetron hydrochloride) injection, for intravenous or intramuscular use Initial U.S. Approval: 1991.

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