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Acute Myocardial Ischemia after Administration of Ondansetron Hydrochloride

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ONDANSETRON hydrochloride (Zofran; Glaxo Wellcome Inc., Research Triangle Park, NC) antagonizes the effect of serotonin at the 5-hydroxytryptamine$_3$ (5-HT$_3$) receptors.[1] Serotonin is released from the enterochromaffin cells of the small intestine, stimulates the vagal afferents through the 5-HT$_3$ receptors, and initiates the vomiting reflex. Through its 5-HT$_3$–blocking effect, ondansetron hydrochloride has been progressively introduced into the practice of anesthesiology to treat perioperative nausea and vomiting. Administration of ondansetron is believed to be safe and is associated with very few reported serious side effects.[1,2] However, we describe a patient with no history of cardiac abnormalities who experienced a severe episode of acute myocardial ischemia that occurred during the intravenous injection of ondansetron in the early postoperative period.

Case Report

A 60-yr-old woman who was a nonsmoker developed slight exertional wheezing. A 2-cm-diameter left lower lobe lung mass with a surrounding infiltrate was found on a chest radiograph and subsequent computed chest tomography, with no lymphadenopathy. A transbronchial biopsy provided the diagnosis of well-differentiated adenocarcinoma with bronchioloalveolar features. She had a medical history of several prior minor operations with no complications. She also reported the subjective feeling of an occasional extrasystole, but no other cardiac symptoms were elicited. She was very physically active, exercising frequently each week in a health club. Her physical examination was entirely normal. The preoperative electrocardiogram (ECG) demonstrated only minimal nonspecific S-T changes. Other than a mild anemia (hemoglobin, 11.5 g/dl), results of her laboratory tests were normal. Pulmonary function testing showed very mild airway obstruction.

The patient (52 kg, 162 cm, American Society of Anesthesiologists physical status II) was scheduled for a left lower lobectomy. On the morning of surgery, a thoracic epidural catheter was placed with no paresthesias, blood, or cerebrospinal fluid return. The patient then underwent an uncomplicated left lower lobectomy and mediastinal lymphadenectomy with general anesthesia; ventilatory separation of the lungs was accomplished with a left-sided double-lumen endotracheal tube. She was easily extubated in the operating room. The initial postoperative course was uneventful. The patient received good pain relief from epidurally administered ropivacaine and fentanyl. The final pathology revealed a 2.1 × 2.0-cm well-differentiated bronchioloalveolar carcinoma involving the visceral pleura, with all lymph nodes free of metastases, staged as T2N0M0 (stage IB).

In the surgical intensive care unit on the first postoperative day while still on continuous ECG monitoring (fig. 1), the patient started to complain of nausea, worse than the mild intermittent nausea present on the day of surgery. She received droperidol 0.625 mg intravenously in three consecutive doses approximately 30 min apart, but without adequate therapeutic effect. Her continuously monitored arterial oxygen saturation on room air at that time was 99%. Because of the continuing nausea, antiemetic ondansetron was prescribed. Immediately after intravenous administration of 2.0 mg ondansetron, the

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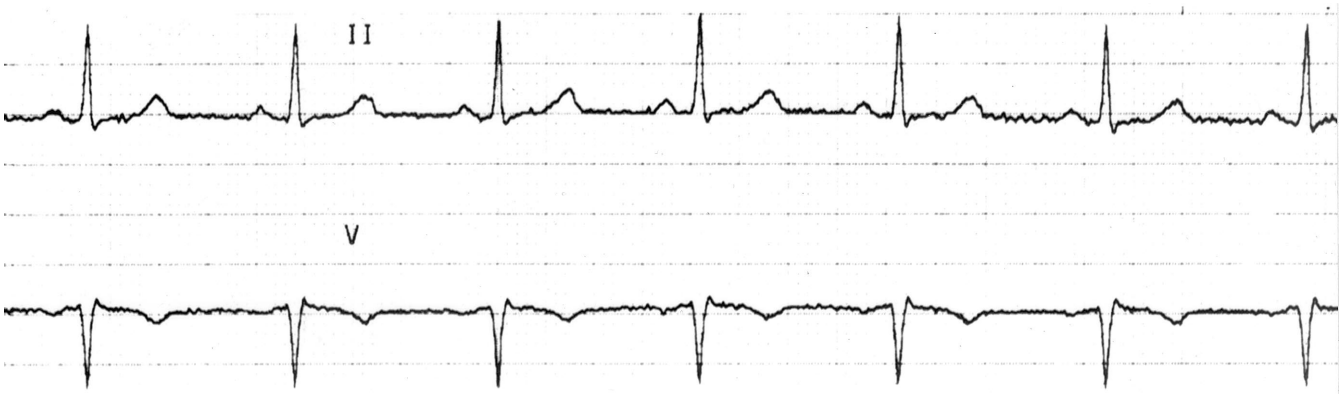

Fig. 1. Leads II and V_2 from the electrocardiogram monitor of the patient in the intensive care unit on the morning of the first postoperative day, 5 h before ondansetron administration.

patient developed severe substernal chest pain, hypertension (158/70 mmHg), marked ST depression in the inferolateral ECG leads, ventricular and supraventricular tachyarrhythmias with a ventricular rate of 178 beats/min, and frequent multifocal premature ventricular contractions that progressed to runs of ventricular tachycardia (fig. 2). Within only a few minutes of receiving 0.4 mg sublingual nitroglycerin, all symptoms resolved, and the ECG abnormalities completely disappeared in < 1 h. Subsequent ECGs were unchanged from the preoperative tracings. Serial serum creatine phosphokinase isoenzyme levels were entirely normal, ruling out any myocardial necrosis. The patient had an uneventful subsequent course and was discharged home asymptomatic on the fourth postoperative day.

After discharge, the patient underwent a complete cardiac evaluation. She underwent cardiac stress testing, exercising 7 min on a standard Bruce protocol, and achieved a maximum heart rate of 150 beats/min, 95% of her predicted maximum. She had no chest pain or ECG changes. Stress and resting single-photon emission computed tomography using 29.5 mCi Myoview (technetium-99m tetrafusmin; Nycomed Amersham Imaging, Princeton, NJ) demonstrated no evidence of ischemia or prior infarction. An echocardiogram demonstrated normal left ventricular systolic function with mild tricuspid and mitral insufficiency. Twenty-four–hour Holter ECG monitoring found rare premature ventricular contractions and premature atrial contractions with three nonsustained runs of asymptomatic supraventricular tachycardia, but no evidence of asymptomatic ischemia. There was no evidence whatsoever of significant anatomic coronary stenosis resulting in ischemia with provocative stress testing. Therefore, cardiac catheterization was not indicated.

Although rare, inferior wall myocardial ischemia may cause nausea as the only symptom. However, there were no ECG changes or symptoms until immediately after ondansetron administration. We concluded, as did our cardiology consultants, that the sudden cardiac event after surgery was most likely ondansetron-induced acute myocardial ischemia, probably from coronary vasospasm that resolved with nitroglycerin.

Discussion

Ondansetron, together with granisetron, dolasetron, and tropisetron, belong to the group of 5-HT_3 and 5-HT_4 receptor inhibitors.[1–3] The 5-HT_3 receptor complex is comprised of multiple subunits, with the highest density in the brain (preoptic area, nucleus tractus solitarius, brainstem areas, area postrema) and in the periphery (proximal colonic wall).[4,5] Stimulation of 5-HT_3 and

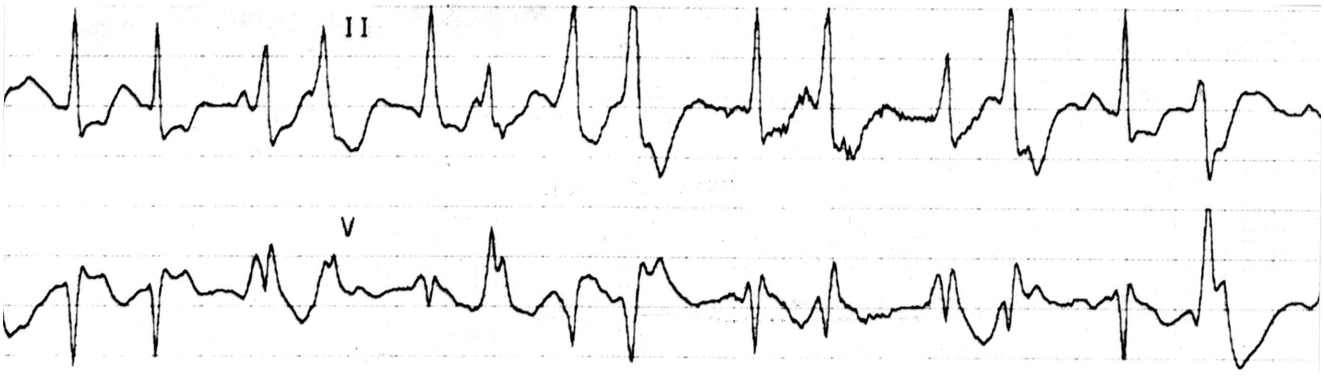

Fig. 2. Electrocardiogram monitor record of the same leads shown in figure 1 5 min after the administration of ondansetron. The patient was having ongoing substernal chest pain at the time this strip was recorded.

5-HT_4 receptors with serotonin in the brain or at the periphery causes nausea and vomiting, alters sympathetic activity by modulating the vagal bradycardia evoked by activation of the von Bezold-Jarisch reflex in anesthetized rats,[6] and contributes to the activation of abdominal sympathetic afferents in cats.[7]

Despite its excellent record of safety, serious side effects associated with ondansetron, such as vascular occlusive events, have been reported in cancer patients. In 1992, Ballard *et al.*[8] reported the first clinical cases of ondansetron-associated myocardial events in patients undergoing chemotherapy. Of the seven patients in their brief report, four had a history of coronary artery disease. Five had multiple episodes of angina usually relieved by nitroglycerin, but one patient died with one anginal attack.

In 1997, Baguley *et al.*[9] described two patients in the perioperative period who received prophylactic ondansetron and metoclopromide for a history of severe anesthesia-associated nausea and vomiting. One patient in the preoperative holding area received the drugs and developed lightheadedness and nausea, which progressed to chest heaviness, ventricular bigeminy, and ST- and T-wave changes that eventually resolved spontaneously with no evidence of an acute myocardial infarction. The other patient was already anesthetized and first received metoclopromide and 20 min later ondansetron, which immediately resulted in ventricular and atrial tachyarrhythmias that eventually resolved with esmolol. The presence of metoclopromide along with ondansetron in these two cases confounds any attempt to conclusively link these cardiac events to ondansetron alone, but the association is certainly suspected.

There is no clear explanation of how the serotonin antagonist ondansetron might precipitate myocardial ischemia and arrhythmias. However, Saxena and Villalon,[10] in their review of the cardiac effects of serotonin, may provide a potential mechanism. The main response initially to 5-HT is a short-lasting bradycardia, mediated *via* a Bezold-Jarisch–like reflex, probably initiated by stimulation of 5-HT_3 receptors on cardiac vagal afferents. Once the bradycardia is suppressed, 5-HT then causes cardiac stimulation, depending on the species studied. Sevoz *et al.*[11] also found administration of 5-HT agonists in the rat resulted in a similar cardiodepressant effect *via* the Bezold-Jarisch reflex that was prevented by pretreatment with the 5-HT_3 antagonist ondansetron. In humans and a few other species, Saxema and Villalon[10] reported that a complex pattern of coronary vasodilatation and constriction are mediated by various 5-HT receptors.

Based on these various observations, we would postulate that in some individuals, ondansetron, by suppressing the 5-HT_3 cardiac receptors, may result in inhibition of the Bezold-Jarisch reflex, leading to tachyarrhythmias, which in some cases may also be associated with coronary vasoconstriction, resulting in acute ischemia.

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