Original Article

Bradycardia After Intravenous Ondansetron with Asystole on Rechallenge: A Case Report

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ABSTRACT

Purpose: There have been 3 published reports (4 cases) of symptomatic sinus bradycardia occurring after intravenous (IV) administration of the selective 5-hydroxytryptamine 3 (5-HT₃) receptor antagonist ondansetron. We report a fifth case in which the patient developed asystole after rechallenge with ondansetron.

Summary: A 36-year-old pregnant patient with no cardiac history, status post cerclage for cervical insufficiency, experienced nausea in the post ambulatory care unit after administration of morphine and indomethacin for pain. After IV administration of ondansetron, the patient's heart rate decreased to the 40s and improved spontaneously. The patient experienced a second episode of nausea, another dose of ondansetron was administered, and the patient went into asystole. Advanced cardiac life support measures were initiated and chest compressions were conducted for 3 minutes with return of spontaneous circulation. The patient was monitored overnight with no development of new cardiac arrhythmias and was discharged from the hospital in stable condition.

Conclusions: Sinus bradycardia after IV administration of ondansetron was observed in a 36-year-old pregnant patient status post cerclage. On rechallenge, the patient went into asystole. This case report adds to the available literature regarding ondansetron-induced cardiac arrhythmias and the possibility of asystole upon rechallenge.

Key Words—asystole, bradycardia, ondansetron

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Ondansetron is a selective 5-hydroxytryptamine 3 (5-HT₃) receptor antagonist indicated for the prevention and treatment of nausea and vomiting associated with chemotherapy, radiotherapy, and surgery.¹ 5-HT₃ receptor antagonists have been shown to cause electrocardiographic (ECG) changes in healthy subjects. These ranged from increased PR interval, increased QRS complex duration, and increased heart rate observed with dolasetron to prolonged QT_c interval and decreased heart rate observed with ondansetron.² Between 2011 and 2012, the US Food and Drug Administration (FDA) released a series of safety communications regarding ondansetron and the risk of prolonged QT intervals

leading to torsades de pointes. Ultimately, the FDA required labeling changes to the prescribing information of ondansetron, removing the 32 mg single intravenous (IV) dose of administration and limiting the maximum single IV dose to 16 mg.³

We report a case of bradycardia after IV administration of ondansetron in a pregnant patient followed by asystole on rechallenge.

CASE REPORT

A 36-year-old pregnant patient at 15 weeks of gestation with no past medical history except for an incompetent cervix was admitted to gynecology service for an elective cervical cerclage. She was not

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taking any medications at home and had no known allergies. Surgical history was significant for a suction curettage under general anesthesia many years ago (unknown exact date/time procedure was performed). Patient was classified as American Society of Anesthesiologists (ASA) physical status class 2, and the surgical procedure was defined as clean-contaminated. A basic metabolic panel was conducted the day prior to the scheduled surgery and was within normal limits. Her preoperative vital signs were within range with a temperature of 97°F, pulse rate of 84 bpm, respiratory rate of 16 breaths/min, and blood pressure of 110/60 mm Hg with a mean arterial pressure (MAP) of 77 mm Hg.

The surgery was performed at 1:57 pm and ended at 2:15 pm with no reported complications and minimal blood loss. The patient did not receive any preoperative medications. During the perioperative period, she received lidocaine spinal anesthesia. The patient was then transferred to the post ambulatory care unit (PACU) at 2:30 pm. Postoperative vital signs included a temperature of 98.2°F, pulse rate of 78 bpm, respiratory rate of 18 bpm, and blood pressure of 114/66 mm Hg with a MAP of 81 mm Hg. She received morphine 5 mg IV push at 2:39 pm for a pain score of 8 and ondansetron 4 mg IV push at 3:00 pm for nausea and vomiting followed by ondansetron 50 mg orally at 3:30 pm. She was noted to have a heart rate in the 40s but recovered without any intervention. Shortly thereafter, patient had another episode of nausea and retching in which an additional dose of ondansetron was administered (unknown dose) and the patient went into asystole at 4:57 pm. No other medications were administered.

Advanced cardiac life support (ACLS) measures were initiated and the nurse started chest compressions for 3 minutes, after which the patient had return on spontaneous circulation (ROSC) at 5:00 pm. During asystole, the patient's fingerstick glucose level was 92 mg/dL. Her vital signs after the asystole event were stable and included a pulse rate of 88 bpm and a blood pressure of 123/72 mm Hg. A fetal sonogram was also performed and revealed normal movement and normal fetal heart rate. The patient was transferred to the telemetry unit for overnight observation. Multiple tests were conducted and revealed a normal electrocardiogram and normal echocardiogram; there was no evidence of arrhythmias on overnight telemetry monitoring. The patient was deemed to be stable and was discharged the next day with a follow-up appointment.

DISCUSSION

We present a case of severe symptomatic bradycardia after IV administration of ondansetron 4 mg that is distinguished from similar case reports to date by the fact that the patient was rechallenged and went into asystole. Resolution of symptoms after dechallenge and reappearance of symptoms after rechallenge support a causal relationship between IV ondansetron administration and subsequent sinus bradycardia. The patient's Naranjo adverse drug reaction probability score was 8, indicating a probable association between the reaction and IV ondansetron.⁴

There is evidence that the specific ECG changes observed with individual 5-HT₃ receptor antagonists may derive from each agent's relative cardiac Na⁺ channel- and K⁺ channel-blocking potencies.⁴ One in vitro study showed that ondansetron has the greatest HERG K⁺ channel-blocking potency of the available 5-HT₃ receptor antagonists, possibly accounting for the prolonged cardiac repolarization observed with ondansetron.⁵

It has been suggested that the observed ECG changes are a class effect and not clinically relevant.^{6,7} Yet isolated reports of serious arrhythmias after ondansetron administration continue to appear. These have included one case of atrial fibrillation, one case of T-wave inversion with ST segment depression, and one case of fatal ventricular tachycardia.⁸⁻¹⁰ In addition, there have been 4 reported cases of sinus bradycardia associated with the IV administration of ondansetron.^{8,11,12}

The first case report involved a 32-year-old male patient who presented to the hospital for hardware removal from his right calcaneus.⁸ He had no significant past medical cardiac history except for a 10- to 20-second episode of palpitations 3 months prior to his procedure. He received propofol, lidocaine, fentanyl, and succinylcholine for induction of anesthesia and intubation and was administered cefazolin prior to incision. During the perioperative period, the patient was maintained on desflurane for anesthesia and received IV metoclopramide 10 minutes after incision. Approximately 20 minutes later, with a heart rate at 65 bpm, he received IV ondansetron 2 mg. After administration, his ECG revealed a sinus bradycardia with a heart rate of 50 bpm, which progressed to junctional rhythm of less than 30 bpm with ventricular escape beats. The patient was administered IV atropine 1.2 mg in divided doses, and he went into an episode of accelerated

junctional rhythm followed by sustained ventricular tachycardia that was stopped after administration of IV esmolol. He was discharged from the hospital in stable condition with no cardiology follow-up. The authors concluded that although the cause of the dysrhythmia was unclear as the patient received metoclopramide as well, it may be important to monitor the ECG while a patient is on ondansetron and metoclopramide.

The second and third case reports were published in one article and included one pediatric patient and one adult patient.¹¹ An 8-year-old pediatric patient presented to a tertiary hospital with perianal abscess and was administered IV ondansetron 2 mg. Prior to administration, the patient's heart rate was 120 bpm; within 2 to 3 minutes, the patient became unconscious, apneic, and bradycardic to 16 bpm. Atropine was administered, and the patient was ventilated with 100% oxygen using a mask. The patient regained consciousness and resolution of bradycardia with a heart rate of 130 bpm. A 60-year-old patient with stomach carcinoma was admitted to the hospital for a total gastrectomy. He was premedicated with glycopyrrolate and ondansetron 4 mg (route not specified). After 2 minutes of administration of ondansetron, the patient's pulse rate dropped from 120 bpm to 20 bpm and was associated with respiratory arrest and loss of consciousness. The patient received IV atropine 0.6 mg, and he regained consciousness with a pulse of 100 bpm. The authors suggested that although rare, extreme bradycardia may be associated with ondansetron and cautious use of this medication is warranted.

Finally, the fourth case report involved a 43-year-old female patient of physical status ASA 1 who presented for a laparoscopic cholecystectomy.¹² She denied any history of cardiovascular disease and was not taking any medications or had any known drug allergies. Prior to pre-medications, the patient's heart rate was 86 bpm in normal sinus rhythm. She was administered IV ondansetron 4 mg and within 3 to 4 minutes she complained of faint and giddiness. She ultimately developed respiratory arrest and was in sinus bradycardia at a rate of 24 bpm. Supplemental oxygen was delivered to the patient, and atropine 1 mg total was administered in 2 divided doses. After the second dose of atropine, the patient's heart rate increased to 124 bpm and she regained consciousness.

We report a fifth case of sinus bradycardia after IV administration of ondansetron that resolved spontaneously; it was followed by a second dose of

ondansetron, after which the patient went into asystole. The isolated and apparently idiosyncratic nature of reported cases of ondansetron-induced bradycardia, including the one we report, do not seem to warrant practice change. Clinicians should be aware that such a reaction is a real, if highly unlikely, possibility. Clear risk factors for such episodes remain to be elucidated.

CONCLUSIONS

A patient with no pertinent past medical history developed bradycardia after initial administration of IV ondansetron and recovered spontaneously. Thereafter, she complained of a second episode of nausea and retching; a second dose of IV ondansetron was administered, after which she went into asystole. Ultimately, the patient had ROSC within 3 minutes and was stable for discharge the next day. Clinicians should be aware that sinus bradycardia is a rare but potential adverse effect of intravenously administered ondansetron that can occur at any dose.

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