

CASE REPORT

Rotatory nystagmus after granisetron administration

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ABSTRACT

Background: Granisetron is a popular antiemetic medication used in the emergency department to control nausea and vomiting with an excellent side effect profile among adults and pediatric, in both healthy and oncology patients.

Case Presentation: Our patient received granisetron for nausea and vomiting then developed torsional nystagmus, asymmetrical abnormal muscle contractions, and electrocardiography showed QTc prolongation 487 ms. The patient did improve after IV lorazepam and magnesium sulphate administration.

Conclusion: QTc prolongation increases the risk of developing Torsades de Pointes and sudden death. Extrapyramidal syndrome caused by granisetron is rare and should not be confused with seizure. Both are significant effects associated with 5-HT₃ antagonists administration to be aware of and if they occurred, should be managed in a timely fashion.

Keywords: Antiemetics, granisetron, extrapyramidal syndrome, nystagmus, rotatory nystagmus, QTc prolongation, Torsades de Pointes, beetroot effect.

Introduction

Emesis is produced through the activation of the vomiting center in the brain. The vomiting center is activated through different pathways including efferent signals from higher centers, activation of 5-hydroxytryptamine or serotonin type 3 (5-HT₃) receptors, and dopamine type 2 receptors which are located in the chemoreceptor trigger zone and through the activation of vestibular nuclei. 5-HT₃ receptors are also found on dopaminergic nerve endings in the nucleus accumbens and amygdala. Granisetron is considered more effective and safer than other 5-HT₃ blockers. It is a selective serotonin receptor antagonist that works in the chemoreceptor trigger zone in the brain stem by blocking 5-HT₃ receptors and blocks afferent signals from the vagus nerve in the gastrointestinal tract [1]. Various 5-HT₃ blockers exist, and they differ in their affinity for binding to serotonin receptors. In fact, these medications have an excellent side effect profile. 5-HT₃ blockers are the medication of choice in patients presenting with emesis after chemo or radiotherapy [2]. Granisetron has been used in healthy adults and shown to be efficacious with minimal alterations in vital signs, which made it possible and safe for use in patients who are not receiving chemotherapy. One patient experienced prolonged QT (446 ms) after intravenous administration but without clinical significance. There is an association

between 5-HT₃ blockers and nonselective serotonin agonists that might result in fatal ventricular dysrhythmias. They reported QTc maximum increase for granisetron and ondasetron 401 ± 25 ms and 404 ± 18 ms, respectively [3]. In another randomized clinical trial, 5-HT₃ blockers were studied in pediatric patients on chemotherapeutics that are not toxic to the heart and found that granisetron was unlikely to be arrhythmogenic at low doses of 10 µg/kg, but they noticed reversible bradycardia, PR shortening and incidence and severity of cardiac effects including QTc prolongation is dose dependent [4]. In another prospective interventional study, granisetron was given to patients who were treated with cardiotoxic chemotherapeutic, and they found that intravenous administration, especially at high doses, was associated with significant (but clinically silent) ECG changes

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including bradycardia, A-V block, and QT prolongation. However, this cannot be attributed entirely to granisetron since this population was receiving cardiotoxic chemotherapeutics [5]. A randomized clinical trial was performed by Aapro et al. [6] comparing granisetron with metoclopramide. Six of 130 patients treated with granisetron developed abnormal body movements, but unfortunately it was not clarified whether those patients had brain metastasis, were taking other medications, had electrolyte disturbances or had seizure disorders that could explain the abnormal movements rather than attribute the movements to granisetron. Extrapyramidal manifestations are dependents on dopamine and acetylcholine levels which can be altered by 5-HT3 blockers [7]. Normal QTc in females is below 460 ms. A preexisting prolonged QTc or a value 500 ms or higher or increase by 60 ms from baseline is considered high risk for death and/or Torsades de Pointes [8,9].

Case Presentation

A 43 years old previously healthy woman was transferred to the emergency department (ED) after fainting. She had been doing fine until that morning. She had her regular morning homemade sugared beetroot juice (200 ml) then she started to experience nausea and had repeatedly vomited. She sought medical advice from a colleague in Anesthesia department and was treated with intravenous granisetron HCL 1 mg. Shortly after the injection, she had dizziness, blurring of vision, and presyncope. She was brought immediately to the ED. The vomit was of food content, and there was no hematemesis, and no bilious vomiting. There was no abdominal pain, no bleeding per

orifice, no other gastrointestinal symptoms, no palpitation, no shortness of breath, and no chest pain. She did not completely lose her consciousness but was drowsy and able to hear surroundings. There was no history of similar complaints, cardiac disease, neurological disorder, history of hormonal use, recent surgery or trauma, pulmonary embolism, smoking, drug abuse, or alcohol abuse. She was married and taking folic acid ferrous sulfate supplement. There was no family history of sudden cardiac death. She was regularly exercising multiple days per week. Upon arrival at the emergency department, her vital signs were as follows: blood pressure 115/80 mmHg heart rate 67 beats per minute respiratory rate 19 breaths per minute temperature 36.6°C oxygen saturation 99% room air, and point of care blood sugar = 6.1 millimole per liter. She was conscious, fatigued, and oriented to time, place and person. Her airway, breathing & circulation were optimal. Her chest, abdomen, cardiovascular system, and skin exams were unremarkable with no signs of trauma. Central nervous system exam: Glasgow Coma Scale 15/15, power was 5/5 on all limbs with normal tone and reflexes, sensation was intact, and cranial nerve examination was normal. Electrocardiography (ECG) at 13:20 (Figure 1) showed sinus rhythm with a rate of 81, PR = 98, QT = 420 ms, and QTC = 487 ms with no baseline ECG in the patient's chart to compare with or history of ECG abnormality. Of note, this ECG was done after the administration of Granisetron. She was attached to a cardiac monitor, and the laboratory investigation was withdrawn. Within one hour of presentation, the patient had right eye rotatory nystagmus with on and off asymmetric nonrhythmic involuntary movements in both

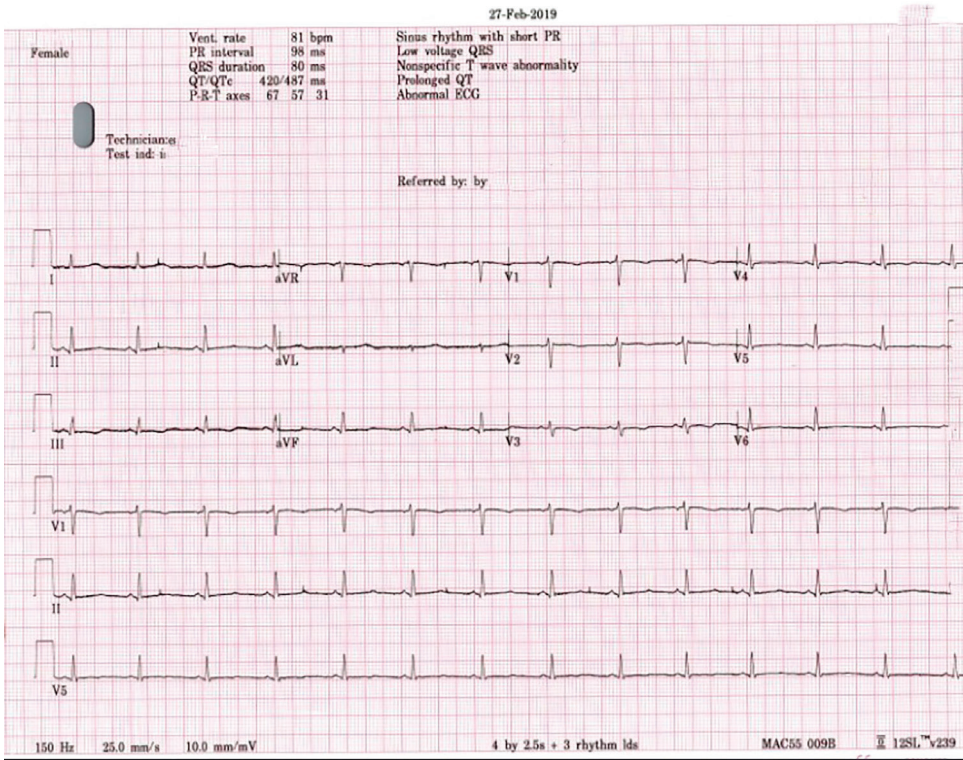


Figure 1. ECG at presentation showing sinus rhythm with a rate of 81, PR = 98, QT = 420 ms, QTC = 487 ms with no previous ECG to compare with or history of ECG abnormality.

upper limbs. Her laboratory values including complete blood count, renal function, highly sensitive troponin I, thyroid function, bone panel and magnesium levels, were within normal range, beta-human chorionic gonadotropin hormone was negative, urine analysis was negative, but creatinine kinase was elevated at 280.

Differential diagnosis is following:

- (1) Drug related extrapyramidal manifestation and QTc prolongation.
- (2) Vasovagal Syncope

Treatment included intravenous normal saline 0.9% 500 ml bolus. Benzotropine was ordered but was out of stock, and we avoided diphenhydramine because of the possibility of further QT prolongation; therefore, lorazepam 1 mg and magnesium sulphate 1 g were administered intravenously. The patient had complete resolution of Nystagmus and extrapyramidal symptoms within thirty minutes of receiving intravenous treatment and repeated ECG after 1 hour (Figure 2) showed normal sinus rhythm with improvements in QT = 396 ms and QTc = 467 ms intervals. The patient was kept for observation for 6 hours with serial ECG, was assessed by cardiology on call and was cleared for discharge. We performed an ECG (Figure 3) prior to discharge and demonstrated normalization of intervals QT = 394 ms and QTc = 454 ms, as shown below. The patient went home ambulating in a stable condition. We followed up the patient two weeks later, she has stopped taking supplementary beetroot and an ECG was performed and demonstrated

sinus rhythm with rate = 78 QT = 420 ms, and QTc = 478 ms with no other significant findings (Figure 4).

Discussion

The use of 5-HT3 antagonists (serotonin type 3 receptor antagonist) has become popular in the ED based on favorable side effect profile and efficacy. Granisetron has been used safely among healthy adults with excellent results. Our patient in this report presented to the emergency department after receiving intravenous granisetron for vomiting and nausea then developed extrapyramidal manifestation in addition to fainting, dizziness, blurred vision, and QT prolongation on ECG. We believe that the nausea and excessive vomiting resulted in a vasovagal response which lead to fainting, dizziness, and blurring of vision. Extrapyramidal syndrome was suggested by rotatory nystagmus and asymmetrical involuntary movements because it was developed after IV granisetron, so we did not consider seizure as a working diagnosis nor ordered CT brain. The patient’s symptoms were alleviated after IV lorazepam. Based on the mechanism of action of 5-HT3 antagonist, we concluded that these symptoms are most likely due to alteration of dopamine levels caused by blocking 5-HT3 receptors located on dopaminergic nerve endings. However, extrapyramidal symptoms attributed to granisetron are rarely reported in the reviewed evidence which was reported in patients receiving chemotherapy while in

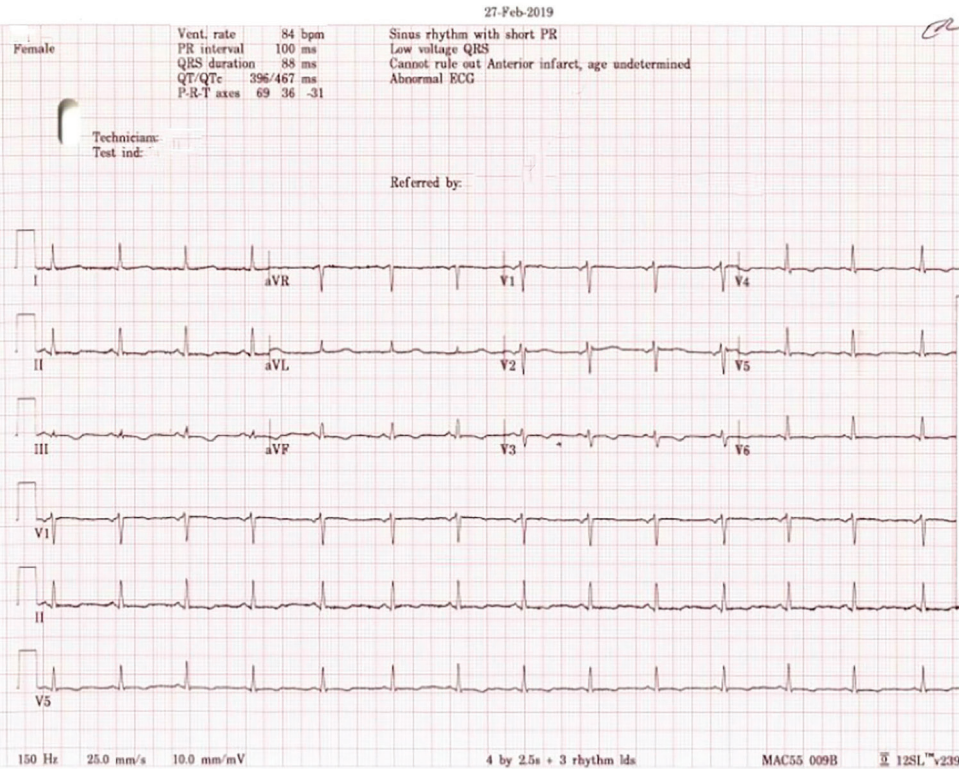


Figure 2. Second ECG after receiving intravenous treatment showing normal sinus rhythm with improvement in QT = 396 ms and QTc = 467 ms intervals.

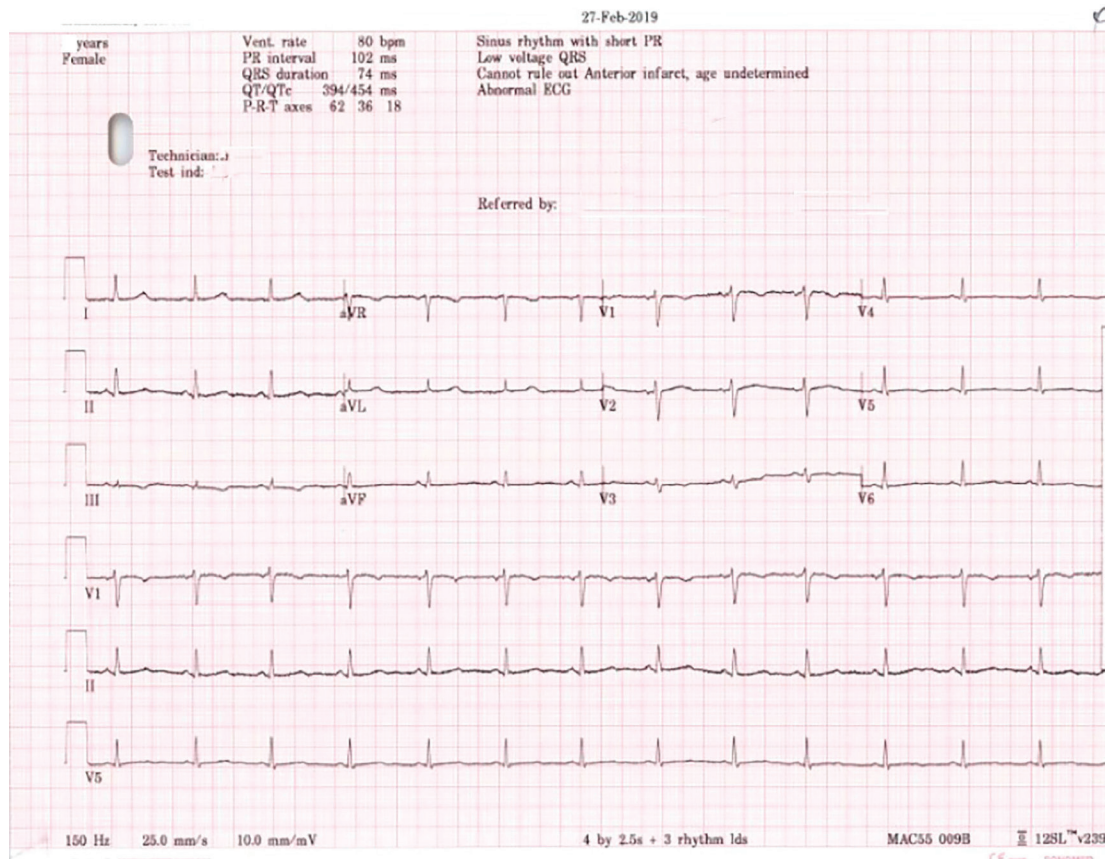


Figure 3. ECG prior to discharge demonstrated normal sinus rhythm and normalization of intervals QT = 394 ms and QTc = 454 ms.

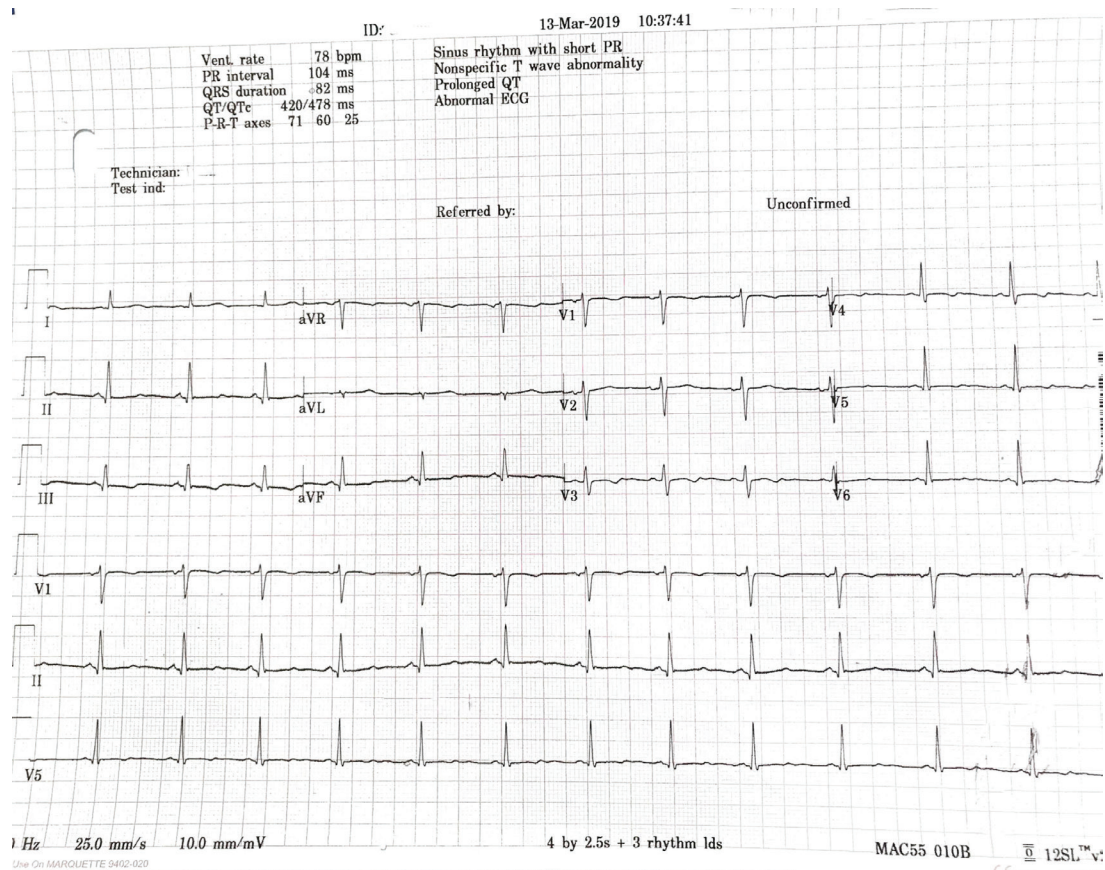


Figure 4. A follow-up ECG two weeks after discharge was performed demonstrate sinus rhythm with rate = 78 with prolonged QT = 420 ms and QTc = 478 ms with no other significant findings.

this case it occurred in otherwise healthy patient aside from the unrecognized QTc prolongation [6,7]. The patient did not have a baseline ECG prior to receiving IV granisetron. And her first ECG in the ED showed prolonged QTc of 487 ms. We repeated the ECG 1 hour later after giving lorazepam and magnesium sulphate, the ECG showed QTc interval improvement and last ECG before discharge showed normalization of QTc. A follow up ECG was done and showed prolonged QTc, suggesting that the patient had a preexisting QT prolongation which was probably increased by administering granisetron. The patient is used to take daily Beetroot juice (200 ml) as a dietary supplement. Beetroot juice intake can increase endurance and delay fatigue resulting from exercise when taken in amount of 6 millimoles. It is one of the most common methods for nitrate supplementation. Supplementary nitrate has the potential to inhibit sympathetic outflow and decrease blood pressure by 5-ml mercury when 0.25 l is consumed (approximately 5.5 millimoles) and by 10-mmHg when 0.5 l is consumed (approximately 22.5 millimoles). It is not considered harmful because of the slow metabolism of nitrate to nitrite. On the other hand, its consumption decreases the use of adenosine triphosphate and oxygen by contracting muscles [10]. Therefore, based on the reviewed evidence, most probably did not result in the presenting complaints. Her symptoms improved after receiving intravenous lorazepam and magnesium sulphate, which supports our diagnosis of medication-related rotatory nystagmus, extrapyramidal manifestations and QT prolongation.

Conclusion

QTc prolongation increases the risk of developing Torsades de Pointes and sudden death. Extrapyramidal syndrome caused by granisetron is rare and should not be confused with seizure. Both are significant effects associated with 5-HT₃ antagonists administration to be aware of and if they occurred, should be managed in a timely fashion.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

None.

Consent for publication

Consent was taken from the patient for publication purposes.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

Learning points/take home messages

- Granisetron administration is associated with rotatory Nystagmus and extrapyramidal syndrome.
- Using Lorazepam and magnesium sulphate in treating granisetron-related rotatory nystagmus, extrapyramidal syndrome and QTc prolongation.

- Obtaining a baseline ECG prior to administering granisetron is advised.
- Beetroot juice consumption is safe and not associated with QTc prolongation or extrapyramidal syndrome based on the reviewed evidence.

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