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CASE REPORT

Ondansetron and Hypothermia Induced Cardiac Arrest in a 97-Year-Old Woman: A Case Report

Keith Sai Kit Leung, BSc[1,a], Faareaha Ahmad[1], Amun Mahmood[1], Yuki Ka Ling Shum, MPharm[1], Ekta Punj, MPharm[2], Azam Majeed, MBBS FRCEM[2], Riad Hosein, MBBS FRCEM[2], Anna Hong, MBChB[2] and Muzaffar Hashmi, MBBS FRCEM[2]

[1]*Faculty of Health and Life Sciences, Aston University, Birmingham B4 7ET, United Kingdom*
[2]*Emergency Department, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham B15 2TH, United Kingdom*

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Abstract

Background: Ondansetron and hypothermia are both known to induce bradycardia or QT interval prolongation, thus placing affected patients at risk of cardiac arrest.
Case Report: Herein, we report the case of a 97-year-old woman who initially presented with confusion and hypothermia, and experienced severe bradycardia and asystolic cardiac arrest after a 4 mg intravenous ondansetron bolus injection.
Conclusion: Ondansetron is associated with bradycardia and QTc prolongation, both of which might be further exacerbated by hypothermia. Clinicians should be aware that administering ondansetron in patients with hypothermia might further increase the risk of adverse cardiac events and eventual cardiac arrest.

Keywords: Ondansetron; Hypothermia; Bradycardia; QT prolongation; Cardiac Arrest

Case Presentation

A 97-year-old woman initially presented to our emergency department (ED) with confusion. She was not able to communicate verbally, and a collateral history was taken from her daughter. Her past medical history included heart failure with preserved ejection fraction, previous neck of femur fracture, gout, and folate and vitamin B12 deficiency anaemia. She had no known family history of sudden cardiac death or congenital arrhythmias. The patient had visited the ED both 8 and 6 days before this presentation, for abdominal pain secondary to constipation, dehydration, and hypercalcaemia. She was discharged 2 days after admission but then returned with reduced oral intake, and passage of dark stool and urine. She was discharged 1 day after admission, and no abnormalities were detected in her blood profile and urinalysis (Table 1).

[a]First Author
Correspondence: **Keith Sai Kit Leung**, Faculty of Health and Life Sciences, Aston University, Birmingham B4 7ET, United Kingdom, E-mail: keithsaikit.leung@nhs.net; **Muzaffar Hashmi**, Emergency Medicine Consultant, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham B15 2TH, United Kingdom, E-mail: muzaffar.hashmi@uhb.nhs.uk; **Anna Hong**, SHO in Emergency Medicine, Queen Elizabeth Hospital Birmingham, University Hospitals, Birmingham NHS Foundation Trust., Birmingham B15 2TH, United Kingdom, E-mail: anna.hong@uhb.nhs.uk

Table 1 Clinical Laboratory and Blood Gas Parameters Before and After Arrest.

Laboratory parameters	Trust reference ranges	Admission 8 days before arrest	Admission 6 days before arrest	1 hour pre-arrest	2 days post-arrest	3 days post-arrest	5 days post-arrest
Na (mmol/L)	133–146	140	141	122	137	135	138
K (mmol/L)	3.5–5.3	3.9	4.1	4.1	3.3	2.8	4.4
Urea (mmol/L)	2.5–7.8	10	7.6	7.7	3.9	4.3	3.6
Creatinine (μ mol/L)	49–90	68	68	67	54	60	53
eGFR (ml/min/1.73m^2)	>90	65	65	66	76	74	77
Bilirubin (μmol/L)	0–9	5	7	8	–	–	–
AlkP (U/L)	30–130	108	111	127	–	–	–
ALT (IU/L)	0–55	35	31	26	–	–	–
Albumin (g/L)	35–50	39	39	38	–	–	–
Calcium (mmol/L)	2.13–2.55	2.6	2.45	–	–	–	–
Corrected calcium (mmol/L)	2.2–2.6	2.65	2.5	–	–	–	–
Total protein (g/L)	60–80	64	67	64	–	–	–
Phosphate (mmol/L)	0.8–1.5	0.95	1.08	–	–	–	0.77
Magnesium (mmol/L)	0.7–1.1	0.85	–	–	0.77	–	0.77
CRP (mg/L)	0–5	6	–	13	128	82	50
Amylase (U/L)	12–125	94	–	–	–	–	–
Ferritin (μg/L)	5.0–204	–	100	–	–	–	–
Hb (g/L)	115–154	120	124	112	108	108	105
WBC (×10^9/L)	3.9–10.9	3.9	4.6	11.5	5.7	6.2	5.2
Plat ($\times 10^9$/L)	150–400	102	99	132	118	134	164
RBC ($\times 10^{12}$/L)	3.9–5.1	3.98	3.99	3.72	3.52	3.49	3.46
HCT (L/L)	0.39–0.45	0.369	0.367	0.341	0.306	0.305	0.307
MCH (Pg)	27–30	30.2	31.1	30.1	30.7	30.9	30.3
MCHC (g/L)	317–340	325	338	328	353	354	342
MCV (Fl)	81–102	92.7	92	91.7	86.9	87.4	88.7
INR	0.8–1.2	NA	0.9	0.9	–	–	–
Folate (μg/L)	3.1–20.5	8.8	–	–	–	–	–

Table 1 Continued

Blood gas parameters	Reference ranges	Pre-arrest VBG	Post-arrest ABG
pH	7.35–7.45	7.324	7.322
FiO_2	–	0.21	0.80
pO_2 (kPa)	11.07–14.40	3.9	54.3
pCO_2 (kPa)	4.27–6.40	8.4	5.9
HCO_3 (mmol/L)	22–29	32	22.5
Base excess	−2 to +2	4.6	−3.5
Anion gap (mmol/L)	10–18	14.4	21.1

After a collateral history was taken, her main presenting complaints were worsening confusion, persistent vomiting of possible faecal matter, and reduced urinary frequency, in addition to her known long-standing poor oral intake and constipation. Bedside observations and vital signs revealed a temperature of 33.8°C, blood pressure of 152/124, heart rate of 66 bpm, respiratory rate of 16 with SpO_2 96% on room air, GCS 12 (E4V2M6), and total NEWS score of 6. Clinical examination revealed normal heart sounds with no added murmurs; bilateral chest rise with equal air entry and no abnormal breath sounds; non-tender abdominal distention, no signs of peritonitis, and sluggish bowel sounds; normal muscle tone and power within the confines of a difficult neurological examination; pupils equal and reactive to light at 3 mm; and bilateral pitting oedema to the mid calves.

Routine blood parameters were analysed, and point of care venous blood gas was assessed. The patient was found to be acidotic (pH 7.32), severely hyponatremic (120 mmol/L), and anaemic (112 g/L), and she had an elevated lactate of 4.08 mmol/L. An ECG was performed, which indicated normal sinus rhythm with HR 60 bpm and a borderline prolonged QTc of 466 ms (Figure 1). A head CT was performed as part of the initial confusion screen, which indicated no acute changes. Given her persistent vomiting, we decided to prescribe her 4 mg IV ondansetron and 1 L 0.9% normal saline slow IVI to correct her hyponatraemia.

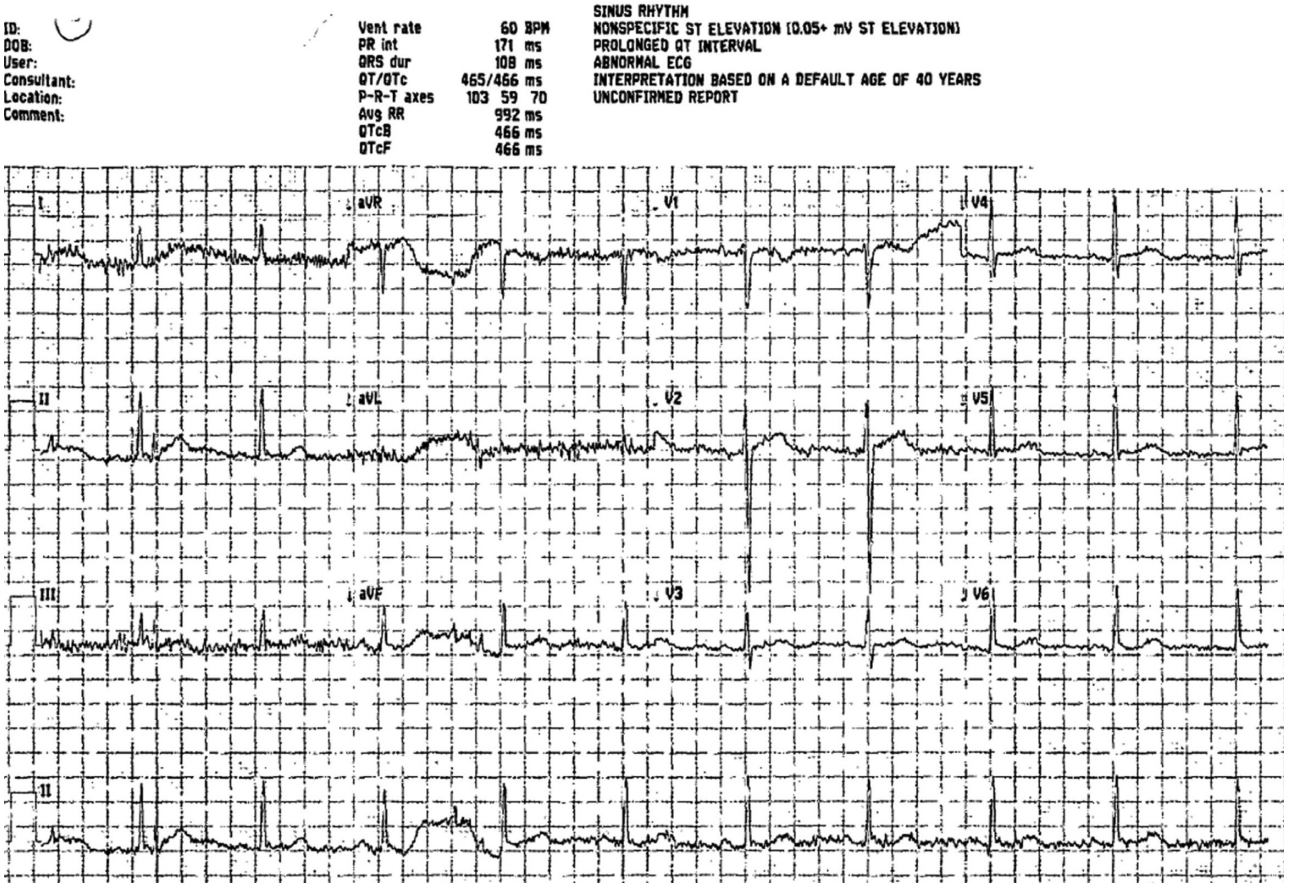

Figure 1 12-Lead ECG 1 Hour Before Arrest, Showing QTc of 466 ms.

Approximately 30 minutes post-administration, she became cyanotic with no breathing effort and unresponsive with GCS 3 (E1V1M1). Continual cardiac monitoring indicated severe bradycardia of approximately 20–30 beats per minute (bpm) followed by asystole. Chest compressions were commenced immediately, an oropharyngeal airway was inserted after suctioning vomitus, and ventilation was started with a Mapleson circuit using a 30:2 ratio. Return of spontaneous circulation (ROSC) was achieved after two cycles of CPR without any pharmacological intervention, with a maximum downtime of 8 minutes.

Investigations

Her post-arrest ECG was normal except for sinus tachycardia of 125 bpm with narrow QRS complexes (Figure 2); arterial blood gas pH of 7.32, sodium of 119 mmol/L, potassium of 2.9 mmol/L, and lactate of 10 mmol/L were observed. Blood parameters before the cardiac arrest are shown in Table 1; the results correlated with the VBG taken earlier. The most recent ECG before admission was reviewed retrospectively, and no QT prolongation was found (Figure 3).

Outcome and Follow-Up

Given the patient's age, frailty, and multiple comorbidities, further escalation of intensive care was deemed futile. DNACPR and agreement to ward based care were established with the family's consent. The patient was treated for aspiration pneumonia, hyponatraemia, and hypokalaemia. She made satisfactory progress clinically and was discharged to a community hospital for further rehabilitation 13 days after the arrest. Ondansetron has now been recorded as a drug allergy for this patient.

Discussion

Ondansetron, a 5-HT_3 receptor antagonist, is one of the most commonly prescribed antiemetics used to treat nausea and vomiting in the ED [1]. According

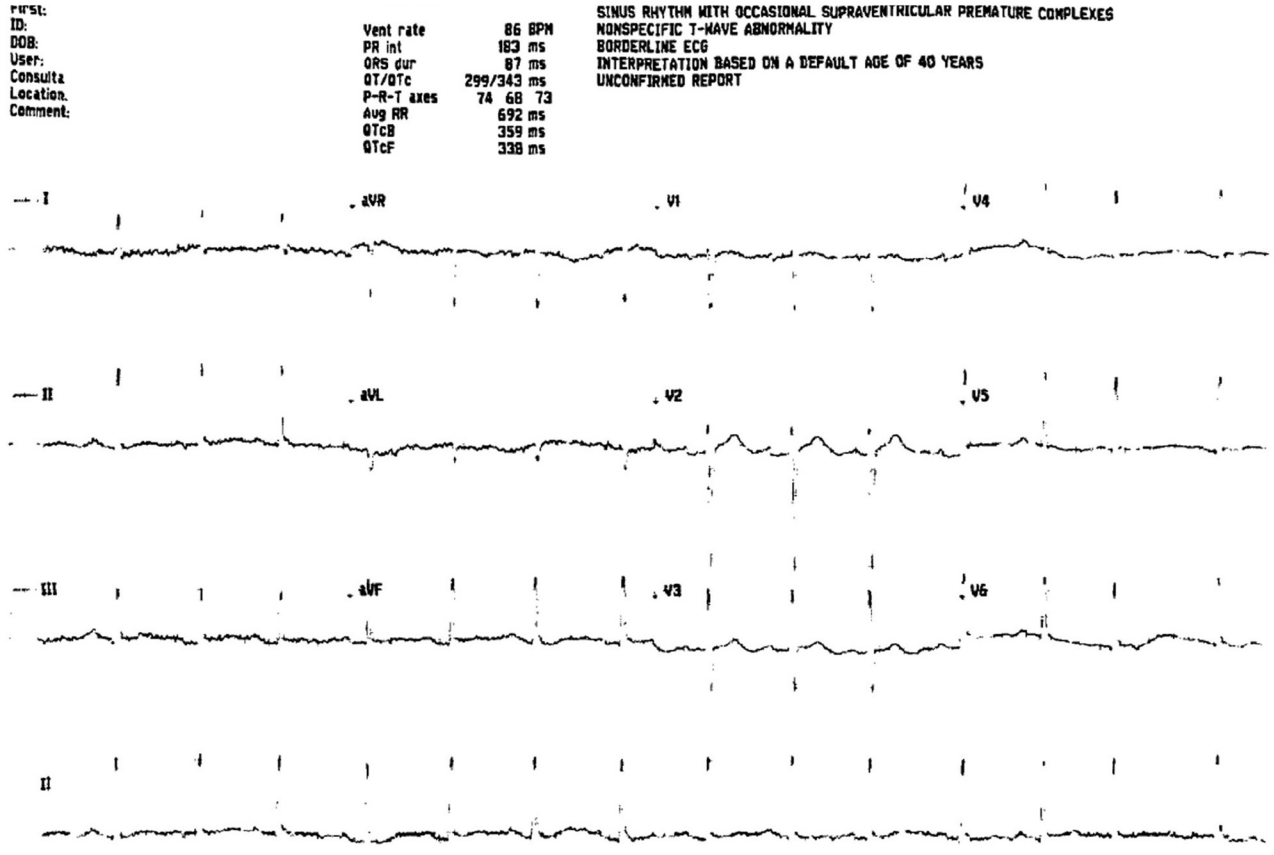

Figure 2 12-Lead ECG Immediately Post-ROSC.

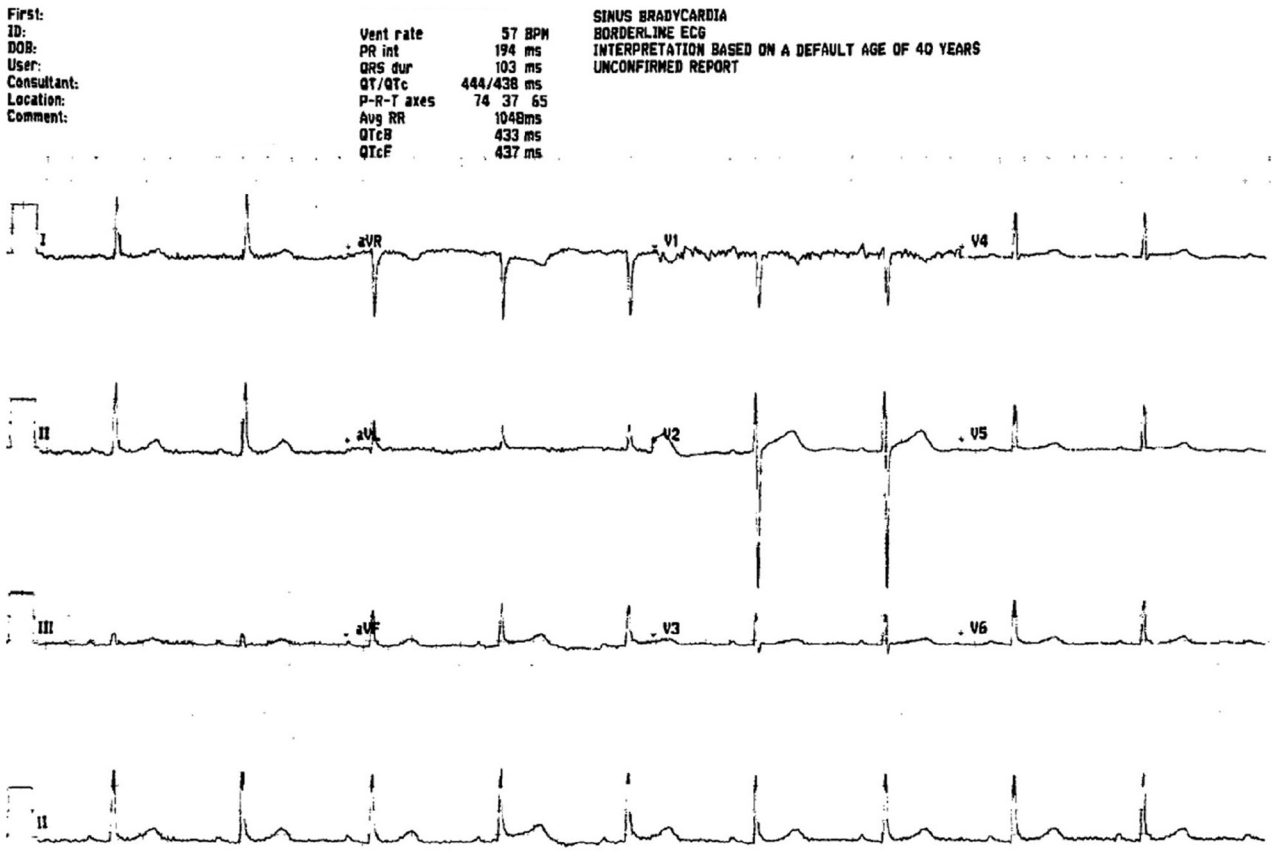

Figure 3 Latest 12-Lead ECG Before Admission, Showing QTc of 438 ms.

to the SmPc, bradycardia and QT interval prolongation are uncommon and rare adverse effects, with an incidence of >1 in 1000 to <1 in 100, and >1 in 10,000 to 1 in 1000, respectively [2], whereas cardiac arrest following ondansetron administration is a very rare adverse drug effect [3]. To our knowledge, this is the first case report in the United Kingdom describing this outcome. QT interval prolongation increases the risk of development of torsades de pointes (TdP) [4]. Several case reports have associated ondansetron with severe bradycardic episodes [5–8]. Interestingly, our patient was also found to have hypothermia, with a temperature of 33.8°C, on initial examination before the arrest. Changes in electrocardiographic parameters are a well-known phenomenon in hypothermic patients, particularly bradycardia and a prolonged QT interval [9–11]. Therefore, we hypothesise two possible mechanisms possibly underlying the arrest in our patient, in which ondansetron use and hypothermia together resulted in 1) severe bradycardia and subsequent asystole or 2) exacerbation of QTc prolongation, thereby resulting in TdP.

The underlying pathogenesis between ondansetron and bradycardia has been proposed to include the Bezold-Jarisch reflex, a cardioinhibitory reflex causing a triad of bradycardia, hypotension and apnoea, which can be paradoxically attenuated by the action of 5-HT_3 receptor antagonists [12]. Notably, among reported cases, a rechallenge with two doses of ondansetron in one 36 year-old woman resulted in initial bradycardia and asystole on second administration [8]. Similarly, our patient became apnoeic and severely bradycardic after ondansetron administration, which preceded her asystolic cardiac arrest. Moreover, several case reports have linked hypothermia, bradycardia, and cardiac arrest under the effect of risperidone, a 5-HT2A receptor antagonist [13]. Although ondansetron acts primarily on 5-HT3 receptors, it has shown to act on secondary lower-affinity binding sites on other 5-HT family receptors [14].

An alternative explanation for the cardiac arrest may underlie by the presence of QT prolongation on initial ECG, as shown in Figure 1, with a QTc of 466 ms. This prolongation might have been caused

by hypothermia, and the subsequent ondansetron bolus might have further prolonged the QT interval, thereby predisposing the patient to the cardiac arrest event. However, we acknowledge that QT prolongation is more commonly associated with tachyarrhythmias, typically TdP, which were not identified in our patient. Instead, she exhibited only a regular narrow complex tachycardia of 125 bpm post-ROSC.

Although these hypotheses appear to be contradictory, both appear to be supported by one case report. Baguley et al. have reported the case of a 34 year-old man who experienced sinus bradycardia instantly after ondansetron administration, which progressed into junctional rhythm with ventricular escape beats, and eventually to accelerated junctional rhythm and supraventricular ventricular tachycardia [5]. We are certain that our patient experienced an episode of severe bradycardia following IV ondansetron, as documented by the reviewing clinician. No further mention was made of changes in arrhythmias, no other observations were taken until post-ROSC as well, until an ECG was taken after downtime of 8 minutes demonstrating a sinus tachycardia. Our patient might possibly have experienced alternative tachyarrhythmias during the interim, but given her acute deterioration and need for resuscitation, no such findings were noted or documented by any medical staff present.

Conclusion

In view of the underlying electrolyte abnormalities with the presentation of hypothermia, a causal relationship could not be established between ondansetron and cardiac arrest in this case. However, in agreement with findings from previous studies, ondansetron may be associated with both bradycardia and QTc prolongation, both of which might be further exacerbated by hypothermia. Clinicians should be aware that administering ondansetron in patients with hypothermia might further augment such risk, and lead to adverse cardiac events and eventual cardiac arrest. Careful history taking and selection of the most appropriate antiemetic is advised, and clinicians are recommended to avoid ondansetron in certain patient groups, as outlined above. A systematic review and meta-analysis of related case series should be performed in the future to gather all available evidence to determine the pro-arrhythmic property of ondansetron.

Consent

Verbal consent was obtained from the patient's next of kin.

Contributors

KSKL was responsible for study conception, project planning, data collection, manuscript drafting, and critical review of the manuscript. AH and MH were involved in medical care of the patient, and were responsible for study conception, project planning, and critical review of the manuscript. FH and AMM performed data collection and critical review of the manuscript. YKLS, EP, AZM, and RH performed critical review of the manuscript.

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Competing Interests

This case report has been accepted and presented in the Intensive Care Society SOA 2022 Congress, and the abstract will be published in the *Journal of the Intensive Care Society*.

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