Effect of a single dose of i.v. ondansetron on QTc interval in emergency department patients

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Purpose. Results of a study to determine whether i.v. administration of a single dose of 4 mg of ondansetron was associated with QT interval prolongation in emergency department (ED) patients are reported.

Methods. In a prospective observational study conducted at an urban academic medical center ED, a convenience sample of adult ED patients treated with ondansetron 4 mg i.v. were enrolled. A 12-lead electrocardiogram (ECG) was obtained immediately before and 5 minutes after ondansetron administration. Measurements of heart rate–corrected QT interval (QTc measurements) provided by ECG machines were evaluated. An electrophysiologist analyzed all ECGs for adverse electrical events and verified the accuracy of QTc values. The primary objective was to measure the QTc change from baseline after ondansetron administration. The secondary objective was to describe adverse electrical cardiac events. Interactions between ondansetron and patients' home medications or ED-provided medications were analyzed.

Results. Among patients included in the data analysis (n = 20), ondansetron administration was associated with a mean QTc increase of 16.2 msec (95% confidence interval, 4.2–28.2 msec; p = 0.01) and a median increase of 12 msec (interquartile range, 5.5–18.0 msec; $p < 0.01$). One patient had a significant cardiac event (pulseless electrical activity) that was likely unrelated to ondansetron use. The home medications of 9 patients (42.9%) were deemed to pose a risk of torsades de pointes, and 17 major QT-prolonging drug–drug interactions were identified.

Conclusion. Significant QTc prolongation occurred in ED patients receiving a single 4-mg i.v. dose of ondansetron. None of the patients had an ondansetron-related cardiac adverse event.

Keywords: adverse event, ondansetron, QTc, safety

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Ondansetron is the most frequently administered antiemetic in emergency medicine. In the United States, ondansetron was given in 12.6 million emergency department (ED) visits between 1995 and 2009.[1] However, in September 2011 the Food and Drug Administration (FDA) issued a warning cautioning that ondansetron may increase the risk of fatal arrhythmias through prolongation of the QT interval.[2]

Most studies examining ondansetron-associated QT prolongation are from the anesthesia literature in the postoperative and perioperative settings.[3-5] In these studies, ondansetron's effect on the QT interval was often confounded by the concomitant use of anesthetics and by procedure-induced hypothermia, and the collected data may not be directly applicable to the ED population. Additionally, ED patients are often undifferentiated—their underlying medical concerns are, at first, unknown—and medications may be given without complete knowledge of the patient's medical

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history, cardiac disease, or prior medication use. Many patients treated in the ED do not have a baseline electrocardiogram (ECG) obtained prior to administration of ondansetron, and the providers may be unaware of underlying asymptomatic long QT syndrome. There is little published evidence regarding the effect of ondansetron on the QT interval during the usual care of ED patients. A single study addressed prolongation of the heart rate–corrected QT interval (QTc interval) in ED patients receiving ondansetron.[6] The study showed a mean 5.2% increase in the QTc interval after ondansetron administration (mean increase, 20 msec), and the authors concluded that this prolongation was of questionable clinical relevance.

The primary objective of the study described here was to measure the change in the QTc interval after administration of i.v. ondansetron in an undifferentiated patient treated in the ED.

KEY POINTS

- A prospective, observational study of ondansetron's effect on the QTc interval in undifferentiated patients treated in the emergency department of an academic medical center was conducted.
- Administration of a single 4-mg dose of i.v. ondansetron was associated with statistically significant QTc interval prolongation; however, the clinical relevance of this prolongation is unknown.
- A majority of patients who received ondansetron were taking QTc interval–prolonging medications.

Methods

We conducted a prospective observational study at an urban, academic, tertiary care adult medical center ED with 45,000 patient visits per year, enrolling patients between June and December 2015. The study was approved by the local institutional review board, and all participants provided written informed consent.

Study population. We included a convenience sample of adult ED patients, according to investigator or research staff availability, who received a 4-mg dose of i.v. ondansetron. We excluded any patient who was critically ill; required an immediate intervention (e.g., for stroke or ST-elevation myocardial infarction); received ondansetron in a dose other than 4 mg, by a route other than i.v., or before arrival to the ED; was pregnant or a prisoner; was unable or refused to give consent; or did not speak English.

Study protocol. At the study site ED, all nonresuscitation medications are ordered via the Epic prescriber order-entry system (Epic Systems, Verona, WI). ED clinical pharmacists prospectively verify most nonurgent medications prior to administration. In the evaluated cases, ondansetron was ordered by treating ED physicians based on usual care practices, and no indications were specified. An ED pharmacist screened all orders and alerted a researcher when an order for i.v. ondansetron was placed, after which a researcher approached the patient and performed a secondary screen for eligibility. The risks and benefits of the study were explained, and written consent was obtained.

After enrollment, 10 electrodes were placed on the patient's chest, arms, and legs. A 12-lead portable ECG machine (MAC 5500, GE Healthcare, Chicago, IL) was used to obtain a baseline ECG immediately prior to administration of ondansetron. The QTc value was recorded from the machine's automated reading. The electrodes and ECG wires were left in place, and a repeat ECG was obtained 5 minutes after ondansetron was given. The pre- and post-ondansetron ECGs were performed by research personnel, who had been trained on appropriate placement of electrodes and use of the ECG machine. Since an ECG might not have been ordered as part of standard ED care for any particular patient, the study protocol called for all study ECGs to be authorized by the treating attending physician and to be immediately evaluated for life-threatening arrhythmias. The rate of ondansetron administration was not controlled, and the drug was given per usual practice. The timing of post-ondansetron ECG acquisition was intended to capture ondansetron's pharmacokinetic peak and minimize interference with patient care. All cardiac adverse events, such as changes in heart rate or rhythm, were recorded.

The automated QTc values were supplemented by manual evaluation of all study ECGs by an electrophysiologist. The tangent method, using lead II, was used to determine the end of the T wave, which allowed measurement of the QT interval. A line (tangent) was drawn from the peak of the T wave to the steepest point of the descending limb of the T wave. The end of the T wave was defined as the point where the tangent line intersected the isoelectric baseline. U waves were excluded from QT interval measurement. QTc values were manually calculated using Bazett's formula and compared with the machine-provided values. Further, all post-ondansetron ECGs were evaluated for adverse or significant electrical changes. During manual ECG evaluation, the electrophysiologist was blinded to patient demographics, past medical histories, and concurrent medications but was not blinded to machine-provided QTc values.

Patients not admitted to the hospital as inpatients were followed until they left the ED. Admitted patients were followed for 1 week during hospitalization to monitor for cardiac events. Inpatient cardiac events were obtained from a review of daily progress notes and significant events notes. ECGs during hospitalization were not evaluated.

We also collected demographic information for each patient, including age, sex, presenting complaint, past medical history, past surgical history, laboratory values, disposition (admission and discharge status), end diagnosis, and ED medications given during the ED stay. To obtain the most current home medication list, medication histories were obtained from each patient through patient interviews and chart review. Patient's home or prehospital medications and those administered in the ED prior to ondansetron use were evaluated for drug–drug interactions using the Micromedex 2.0 Drug Interactions database (Truven Health Analytics, Greenwood Village, CO). The drug interactions were then classified as mild, moderate, major, or "contraindicated" (i.e., warranting a contraindication to use of the offending drug) according to the severity of the documented drug–drug interaction. Further, all medications were evaluated for their QT-prolonging potential via the CredibleMeds website (www.crediblemeds.org; AZCERT, Inc., Oro Valley, AZ).[7] This evidence-based rating tool identifies drugs as those for which the risk of torsades de pointes (TdP) is known, possible, or conditional. It also identifies drugs that should be avoided in patients with congenital long QT syndrome. Serious cardiac events (i.e., cardiac arrest, TdP, and ventricular tachycardia or fibrillation) were evaluated for ondanestron causality using the adverse drug reaction probability scale of Naranjo et al.[8]

Outcomes measures. Our primary outcome was the change in QTc interval after ondansetron administration. Here we also describe adverse electrical cardiac events resulting after ondansetron administration and drug–drug interactions between ondansetron and patients' home medications or medications administered during the ED stay.

Statistical methods. Prior to initiation of the study, a power calculation was done to estimate the minimal sample size required. Estimates of both effect size (i.e., a QTc increase of 19.3–27.6 msec) and an appropriate S.D. range (i.e., ±15–20 msec) were based on previous studies.[3,4,9] We calculated that a minimum of 10 patients would be sufficient to detect a prolongation in QTc of at least 20 msec assuming an S.D. of 15–20 msec (α = 0.05, power = 0.8). All statistical tests and analyses were performed with the open-source software package R 3.2.2. The a priori level of significance was set at 0.05. Results are presented as means with S.D. or medians with interquartile range (IQR), as appropriate, for evaluation of continuous variables. The change in QTc was assessed using a 1-sided Wilcoxon signed rank test and a paired *t* test.

Results

We enrolled 21 patients in the study, but 1 patient was excluded from the data analysis when it was discovered that ondansetron had been administered en route by emergency medical services. The median patient age was 52 years (IQR, 43–58 years), and 8 (40%) of the patients were women. Twelve patients (60%) were admitted to the hospital. This admission rate was higher than the overall baseline admission rate for the study ED (approximately 30%). Additional demographics are displayed in Table 1.

The mean ± S.D. pre- and post-ondansetron QTc intervals were 442 ± 37 and 458 ± 48 msec, respectively. The median (IQR) pre- and post-ondansetron QTc intervals were 430 (412–471) and 446 (430–471) msec, respectively. The QTc interval increased after ondansetron use by a mean of 16.2 msec (95% confidence interval [CI], 4.2–28.2 msec; $p = 0.01$) and by a median of 12.0 msec (IQR, 5.5–18.0 msec; $p < 0.01$). Post hoc calculation showed an achieved power of 0.85. The post-ondansetron ECG was obtained at a median of 5 minutes (IQR, 5–5 minutes; range, 4–14 minutes) after ondansetron was given. Extreme QTc prolongation occurred in patients 1, 12, and 20 (Table 2). With the exclusion of those 3 patients from the analysis, the median post-ondansetron QTc prolongation was 10 msec (IQR, 5–15 msec; $p < 0.01$). Patient 18 experienced a major cardiac event unlikely to have been related to ondansetron use. Details about these 4 patients are provided below.

Patient 1 was a 53-year-old man with severe abdominal pain who received ondansetron before laboratory results were available. His medical history was significant for hemodialysis 3 days per week, atrial fibrillation, hypertension, and *Clostridium difficile* colitis treated with oral antibiotics. The patient's first ECG, obtained prior to ondansetron administration, was notable for QRS interval widening (101 msec) and a spike in T waves. Administration of ondansetron resulted in QTc prolongation by 58 msec and no change in the QRS interval. The patient's underlying rhythm was atrial fibrillation. Subsequently reported laboratory results showed hyperkalemia (a serum potassium concentration of 6.4 meq/L). A possible QTc-prolonging home medication was levofloxacin.

Patient 12 was a 55-year-old man with chest pain and nausea. His medical history was significant for atrial flutter, hypertension, end-stage renal disease, kidney transplantation, and transient ischemic attack. Home medications that might have prolonged the QTc included amiodarone, trimethorprim–sulfamethoxazole, and tacrolimus. The machine-provided ECG results showed a QTc increase of 72 msec after ondansetron administration. The electrophysiologist accounted for the patient's underlying rhythm of atrial flutter and determined the increase in QTc to be 28 msec.

Patient 20 was a 35-year-old man with fever, weakness, nausea, and vomiting. His medical history was significant for testicular cancer, human immunodeficiency virus infection, and chronic back pain. Possible QTc-prolonging home medications included methadone hydrochloride 185 mg by mouth once daily. Labo-

ratory results revealed hypokalemia (serum potassium, 3.4 meq/L) and a hemoglobin concentration of 4.2 g/dL. The patient was subsequently diagnosed with acute myeloid leukemia. The patient's underlying rhythm was normal sinus rhythm. The QTc increased from 519 msec before ondansetron administration to 620 msec 12 minutes after ondansetron was given.

Patient 18 was a 51-year-old, 122-kg male with severe recurrent diabetic ulceration of the left foot that had not responded to outpatient antibiotic therapy. His medical history was significant for poorly controlled diabetes mellitus and multiple toe amputations. At presentation, the patient was tachycardic and febrile, with improvement after initial fluid administration. His initial serum lactate concentration was 5.8 mmol/L with an anion gap of 17 meq/L. His initial cardiac rhythm was sinus tachycardia (heart rate, 116 beats/min), and his QTc increased by 10 msec after ondansetron administration. An X-ray revealed extensive subcutaneous emphysema in the left foot and calf, and the surgery team was emergently consulted for necrotizing fasciitis. The patient was given cefepime 2 g i.v., clindamycin 900 mg i.v., and vancomycin 2 g i.v. Ten minutes into the vancomycin infusion (and 150 minutes after ondansetron administration), the patient began to develop redness, itchy rash, and wheezing. The vancomycin infusion was stopped, but the patient became unresponsive and pulseless. Cardiopulmonary resuscitation (CPR) was initiated. The cardiac rhythm was initially recorded as pulseless electrical activity. The patient received 2 rounds of CPR and epinephrine 2 mg i.v., with subsequent return of spontaneous circulation and baseline mental status. The patient was taken into surgery and developed atrial fibrillation on postoperative day 2, with spontaneous conversion to normal sinus rhythm on postoperative day 3. One month after the cardiac arrest, the patient had no further episodes of atrial fibrillation.

Table 1. Patient Demographics (n = 20)

Variable[a]	Value
Median age, yr (IQR)	52 (43–58)
No. (%) female	8 (40)
Race or ethnicity, no. (%)	
White	8 (40)
African-American	5 (25)
Latino	3 (15)
Asian	2 (10)
Other	2 (10)
Significant cardiac history, no. (%)	
Hypertension	11 (55)
Diabetes mellitus	5 (25)
Heart failure	1 (5)
Atrial fibrillation	1 (5)
Other	7 (35)
Chief complaint, no. (%)	
Abdominal pain	6 (30)
Nausea, vomiting, or diarrhea	4 (20)
Dizziness	2 (10)
Other	8 (40)
Pertinent laboratory values, median (IQR)	
Hemoglobin (g/dL) (n = 19)	12.3 (11.2–13.9)
Hematocrit (%) (n = 19)	37.3 (35.1–42.5)
Serum calcium (mg/dL) (n = 14)	9.2 (8.8–9.5)
Serum potassium (meq/L) (n = 19)	4.3 (3.7–4.7)
Disposition, no. (%)	
Admitted to hospital (unit other than ICU)	11 (55)
Admitted to ICU	1 (5)
Discharged from ED	8 (40)

[a]IQR = interquartile range, ICU = intensive care unit, ED = emergency department.

Application of the probability scale of Naranjo et al.[8] yielded a score of 1, indicating that ondansetron was a doubtful cause of the patient's cardiac arrest, which, along with postoperative development of atrial fibrillation, was likely due to other causes, including necrotizing fasciitis, severe sepsis, anaphylactic shock, and surgery.

According to the Micromedex 2.0 database, there were a total of 17 major drug–drug interactions between ondansetron and patients' home medications or medications given in the ED prior to ondansetron. There was 1 contraindication: A patient who was taking ziprasidone received ondansetron (contraindicated per ziprasidone labeling). Further, 9 patients who received ondanestron were already taking home medications known to increase the QT interval and clearly associated with TdP (Table 2).

Discussion

Overall, a 4-mg i.v. dose of ondansetron in the ED resulted in significant QTc interval prolongation. However,

Table 2. QTc Values and Factors Possibly Contributing to QTc Prolongation in the Study Population (n = 20)[a]

Patient[b]	Age (yr)	Sex	Pre-Ondansetron QTc (msec)	Post-Ondansetron QTc (msec)	QTc Change (msec)	Home Medications With QTc Implications (Classification)[c]	Home or ED Drugs Interacting With Ondansetron[d]
1[e]	53	M	396	454	58	Levofloxacin (1), albuterol (4)	Levofloxacin
2	59	M	397	407	10	None	None
3	19	M	399	415	16	Hydrocodone (2)	None
4	47	M	408	422	14	Albuterol (4)	None
5	33	F	409	428	19	None	None
6	63	F	414	439	25	Escitalopram (1), venlafaxine (2)	Venlafaxine, escitalopram
7	51	F	421	415	–6	None	None
8	54	M	423	435	12	Ziprasidone (3)	Ziprasidone[f]
9	57	M	427	433	6	Azithromycin (1), trimethoprim–sulfamethoxazole (4), tacrolimus (2)	Azithromycin, tacrolimus
10	38	F	428	432	4	Azithromycin (1), levoalbuterol (4), trimethoprim–sulfamethoxazole (4), tacrolimus (2)	Azithromycin, tacrolimus, prochlorperazine
11	72	F	432	449	17	None	None
12[g]	55	M	434	462	28	Amiodarone (1), trimethoprim–sulfamethoxazole (4), tacrolimus (2)	Amiodarone, tacrolimus
13	66	M	452	467	15	Trazodone (3)	None
14	70	F	455	460	5	None	None
15	37	F	469	475	6	Sertraline (3)	None
16	43	M	472	443	–29	Albuterol (4), aripiprazole (2), salmeterol–fluticasone (4), methadone (1)	Methadone, aripiprazole
17	51	M	480	492	12	Albuterol (4), formoterol–budesonide (4), citalopram (1), mirtazapine (2), trazodone (3)	Citalopram, trazodone
18	51	M	482	492	10	Salmeterol–fluticasone (4), albuterol (4)	None
19	55	M	512	513	1	Furosemide (3), pantoprazole (3), venlafaxine (2), methadone (1)	Methadone, venlafaxine
20	35	M	519	620	101	Methadone (1)	Methadone

[a]QTc = corrected QT interval, ED = emergency department, M = male, F = female.

[b]Unless otherwise noted, the pre-ondansetron electrocardiogram showed sinus rhythm.

[c]Classification from CredibleMeds: 1 = known risk for torsades de pointes (TdP), 2 = possible risk for TdP, 3 = conditional risk for TdP, 4 = drug to avoid in congenital long QT syndrome.

[d]Drug interactions were evaluated using Micromedex 2.0 Drug Interactions database (Truven Health Analytics). Unless otherwise indicated, interactions for all study patients were classified as major (other possibilities included mild, moderate, and contraindicated) for adding to ondansetron's effect of prolonging the QTc interval.

[e]Pre-ondansetron rhythm was atrial fibrillation.

[f]Ziprasidone considered contraindicated because of interaction with ondansetron.

[g]Pre-ondansetron rhythm was atrial flutter with variable atrioventricular block.

no patient who had ondansetron-associated QTc prolongation had a change in cardiac rhythm or rate or experienced a cardiac event attributable to ondansetron. Two patients had shortening of QTc after ondansetron was given.

Published literature reflects differences of opinion regarding what constitutes normal QTc values. Generally, QTc intervals of <440 msec in men and <460 msec in women are considered normal.[10] According to FDA, QTc prolongation has been associated with increased susceptibility to TdP; however, FDA agrees that the QTc interval is an imperfect qualitative measure of proarrhythmic risk.[11] FDA considers a drug-associated QTc increase of 5–10 msec as a threshold for regulatory concern, while during clinical trials a QTc of >500 msec and a QTc increase of ≥60 msec are used as markers for study drug discontinuation.[11] In clinical practice, QTc interval increases of as little as 20 msec are considered significant by expert opinion.

In 2016, Moffett et al.[6] described a study similar to ours, but our group was unaware of it during the development of our protocols and enrollment. That prospective and observational study involved 22 adults receiving a single 4-mg i.v. dose of ondansetron in 1 ED. The investigators reported a mean ondansetron-associated QTc prolongation of 20 msec (95% CI, 14–26 msec), with no reported serious adverse cardiac events. Moffett et al. excluded patients with a baseline QTc of >450 msec, cardiac conduction abnormalities (e.g., bundle branch block, ventricular preexcitation), or signs of left ventricular hypertrophy with repolarization abnormalities. In contrast, our patients were representative of general ED practice, whereby ondansetron is given with little to no knowledge of medical history, cardiac abnormalities, or baseline QTc intervals; our study also involved a longer follow-up period, including both the ED course and hospitalization. Additionally, in contrast to the study by Moffett et al., in our study an electrophysiologist independently reviewed all ECGs to confirm machine-generated QTc measurements and significant ECG changes.

The mean age of patients in our study was 50 years, as compared with a mean age of 32 years in the study by Moffett et al.[6]; our patients had a longer mean pre-ondansetron QTc interval (442 msec) than those of Moffett et al. (mean, 395 msec). The overall older age of our patients correlated with a higher frequency of comorbidities; furthermore, 3 (15%) of our patients had received an organ transplant and were taking QTc-prolonging medications daily. Overall, our patients' high admission rate, older age, and increased rate of comorbidities made our cohort a high-risk population. The lack of adverse cardiac outcomes in our study is reassuring with regard to the general use of 1-dose ondansetron in emergency medicine.

Previous studies have shown a maximal QTc prolongation at 5 minutes after administration of 4 mg of i.v. ondansetron.[9,12] Based on these prior studies, for our study 1 data point (QTc at 5 minutes) was chosen for ease of collecting reliable data and to decrease interference with direct patient care. In contrast, Moffett et al.[6] recorded ECGs every 2 minutes for 20 minutes after ondansetron administration. In their study, maximal QTc increases occurred at minutes 6, 12, and 14, with maximum mean prolongation occurring at around 6 minutes, which further supports our use of a single data point.

Our QTc values were obtained from machine-automated calculations. These automated calculations have the advantage of being instant, objective, and, most importantly, are commonly used for clinical decision-making. Although manual calculation of the QTc may produce more accurate results due to patient-specific variation in RR intervals, it is time-consuming, inconsistently performed, and subject to interpreter error. We used computer-calculated values because they are most generalizable to standard ED practice, and only 1 set of machine-provided values (in patient 12, as described above) was changed by the electrophysiologist. For that patient, who had atrial flutter, the electrophysiologist changed the pre-ondansetron QTc from 443 to 434 msec and the post-ondansetron QTc from 515 to 462 msec. Secondary analysis resulted in no changes to the interpretation of our patients' pre-ondansetron heart rates or rhythms.

Our mean results for QTc prolongation after ondansetron administration are similar to reported results of previous studies. Charbit et al.[3] evaluated 85 patients with postoperative nausea and vomiting who received ondansetron 4 mg i.v. and found a mean lengthening of QTc of 20 msec. A 2008 follow-up study of 16 healthy volunteers found a mean increase in QTc of 24 msec after ondansetron administration.[13] Another study, by Hafermann et al.,[4] focusing primarily on cardiac patients found that the QTc interval was prolonged by a mean of 19 msec for all patients treated with ondansetron.

The primary limitation of our study was the small sample size, which limited our ability to detect unusual events, such as dysrhythmias. The study was a single-center study at an academic tertiary care ED, which may limit its generalizability. While no recorded cardiac events were attributed to ondansetron administration, our sample size was not powered to capture a potential effect of ondansetron on TdP risk. Our ability to obtain a repeat ECG at exactly 5 minutes after administration of ondansetron was limited due to provision of standard patient care. Patient 16 was outside the 5-minute window for repeat ECG acquisition due to acute nursing needs. All attempts were made not to interfere with direct patient care, and that limited the time we were able to observe the study patients.

Conclusion

Significant QTc prolongation occurred in ED patients receiving a single

4-mg i.v. dose of ondansetron. None of the patients had an ondansetron-related cardiac adverse event.

Disclosures

The study was funded by the University of California San Francisco Resident Research Fund, which played no role in the study. The authors have declared no potential conflicts of interest.

References

1. Tay KY, Ewald MB, Bourgeois FT. Use of QT-prolonging medications in US emergency departments, 1995-2009. *Pharmacoepidemiol Drug Saf*. 2014; 23:9-17.
2. Food and Drug Administration. FDA drug safety communication: abnormal heart rhythms may be associated with use of Zofran (ondansetron) (2011). www.fda.gov/Drugs/DrugSafety/ucm271913.htm (accessed 2016 Aug 8).
3. Charbit B, Albaladejo P, Funck-Brentano C et al. Prolongation of QTc interval after postoperative nausea and vomiting treatment by droperidol or ondansetron. *Anesthesiology*. 2005; 102:1094-100.
4. Hafermann MJ, Namdar R, Seibold GE, Page RL 2nd. Effect of intravenous ondansetron on QT interval prolongation in patients with cardiovascular disease and additional risk factors for torsades: a prospective, observational study. *Drug Healthc Patient Saf*. 2011; 3:53-8.
5. Obal D, Yang D, Sessler DI. Perioperative doses of ondansetron or dolasetron do not lengthen the QT interval. *Mayo Clin Proc*. 2014; 89:69-80.
6. Moffett PM, Cartwright L, Grossart EA et al. Intravenous ondansetron and the QT interval in adult emergency department patients: an observational study. *Acad Emerg Med*. 2016; 23:102-5.
7. Woosley RL, Heise CW, Romero K. QTDrugs list [registration required]. Available from www.crediblemeds.org (accessed 2016 Aug 5).
8. Naranjo CA, Busto U, Sellers EM et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981; 30:239-45.
9. Gupta SD, Pal R, Sarkar A et al. Evaluation of ondansetron-induced QT interval prolongation in the prophylaxis of postoperative emesis. *J Nat Sci Biol Med*. 2011; 2:119-24.
10. Garson A Jr. How to measure the QT interval—what is normal? *Am J Cardiol*. 1993; 72:14B-16B.
11. Food and Drug Administration. E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (2005). www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073153.pdf (accessed 2016 Aug 5).
12. Ganjare A, Kulkarni AP. Comparative electrocardiographic effects of intravenous ondansetron and granisetron in patients undergoing surgery for carcinoma breast: a prospective single-blind randomised trial. *Indian J Anaesth*. 2013; 57:41-5.
13. Charbit B, Alvarez JC, Dasque E et al. Droperidol and ondansetron-induced QT interval prolongation: a clinical drug interaction study. *Anesthesiology*. 2008; 109:206-12.