

# Droperidol and Ondansetron-induced QT Interval Prolongation

## A Clinical Drug Interaction Study

Beny Charbit, M.D.,\* Jean Claude Alvarez, Pharm.D., Ph.D.,† Eric Dasque,‡ Emuri Abe, Pharm.D.,§ Jean Louis Démolis, M.D., Ph.D.,|| Christian Funck-Brentano, M.D., Ph.D.#

**Background:** Droperidol and ondansetron have previously been found to prolong the QT interval in the treatment of postoperative nausea and vomiting. However, this adverse effect has never been confirmed and compared with both drugs under controlled conditions. The objective was to study the effects of droperidol and ondansetron alone or in combination on QT interval duration in healthy subjects.

**Methods:** Sixteen healthy volunteers, eight males and eight females, were enrolled in this prospective, double-blind, randomized, placebo-controlled study. Subjects received 1 mg droperidol, 4 mg ondansetron, 1 mg droperidol plus 4 mg ondansetron, or a placebo, intravenously in a crossover design. Fridericia-corrected QT interval (QTcF) and plasma concentrations were measured repeatedly during 10 h at each study period. The primary endpoint was the maximal placebo time-matched and baseline-subtracted QTcF prolongation ( $\Delta\Delta\text{QTcF}$ ).

**Results:** Compared with placebo, both droperidol and ondansetron significantly prolonged the QTcF interval.  $\Delta\Delta\text{QTcF}$  prolongation was  $25 \pm 8$  ms after droperidol, significantly greater than the  $17 \pm 10$ -ms prolongation with ondansetron ( $P = 0.014$ ). The combination of droperidol and ondansetron significantly increased the mean maximal  $\Delta\Delta\text{QTcF}$  by  $28 \pm 10$  ms. The combination induced greater QTcF prolongation compared with ondansetron alone ( $P = 0.001$ ), but not with droperidol alone ( $P = 0.33$ ). There was no significant pharmacokinetic interaction between droperidol and ondansetron.

**Conclusions:** Under controlled conditions, both droperidol and ondansetron either alone or in combination induced significant marked QTc interval prolongation. However, the combination of both drugs did not significantly increase QTc prolongation compared with that induced by droperidol alone.

\* Assistant Professor, ‡ Research Nurse, || Staff Physician, # Professor, Assistance Publique-Hôpitaux de Paris, Hôpital Saint-Antoine, Service de Pharmacologie; Université Pierre et Marie Curie-Paris 6, Service de Pharmacologie; and Institut National de la Santé et de la Recherche Médicale, Centre d'Investigation Clinique de l'hôpital Saint-Antoine (CIC-9304). † Associate Professor, § Staff Toxicologist, Assistance Publique-Hôpitaux de Paris, Hôpital Raymond Poincaré, Laboratoire de Pharmacologie-Toxicologie, Garches, France.

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Address correspondence to Dr. Charbit: Division of Clinical Pharmacology, St-Antoine University Hospital, 184 rue du Faubourg Saint-Antoine, 75571 Paris Cedex 12, France. beny.charbit@sat.aphp.fr. Information on purchasing reprints may be found at [www.anesthesiology.org](http://www.anesthesiology.org) or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

\*\* <http://www.fda.gov/MedWatch/SAFETY/2001/inapsinc.htm>. Accessed March 11, 2008.

†† <http://www.cfsan.fda.gov/~frf/forum03/T-01.HTM>. Accessed March 11, 2008.

‡‡ <http://www.ich.org/cache/compo/475-272-1.html#E14>. Accessed March 11, 2008.

DROPERIDOL and 5-hydroxytryptamine type 3 receptor antagonists belong to the most effective antiemetics for prevention or treatment of postoperative nausea and vomiting.<sup>1</sup> In 2001, the US Food and Drug Administration issued a “black box” warning regarding the potential for proarrhythmic events related to QT interval prolongation with droperidol use.<sup>\*\*</sup> As a consequence, 5-hydroxytryptamine type 3 antagonists became the most used antiemetics, in particular in the United States.<sup>2</sup> However, setrons share with droperidol the property to block the human ether-a-go-go-related gene (HERG) cardiac potassium channel underlying their theoretical proarrhythmic potential.<sup>3,4</sup> Electrocardiographic data from patients in clinical studies are conflicting.<sup>5–8</sup> In previous reports, White *et al.*<sup>7</sup> failed to demonstrate a statistically significant QT interval prolongation with 1.25 mg droperidol. In a study that was not placebo controlled, we found significant QT interval prolongation with 0.75 mg droperidol but also after 4 mg ondansetron.<sup>8</sup> Despite the weak evidence for cardiac arrhythmic events in the clinical experience accumulated so far with these antiemetics, a new QT study was deemed to be important for a definitive assessment of the effects of these agents on the QT interval. Such a study was requested by the Food and Drug Administration but was stopped because of adverse neurologic effects induced by droperidol.<sup>††</sup>

To assess a drug effect on ventricular repolarization in humans, the International Conference on Harmonisation issued a guideline known as E14.<sup>‡‡</sup> Briefly, the potential for a drug-induced QTc prolongation needs to be assessed in healthy volunteers (when possible) in a crossover placebo-controlled study, allowing to reduce background noise and quantify and compare the magnitude of QT prolongation.<sup>9</sup>

There is increasing evidence that antiemetics should be combined in patients at high risk of emesis in the perioperative period.<sup>1,10</sup> Moreover, in case of failure of one antiemetic, it is recommended to add an agent of another pharmacologic class in combination with the first agent. Therefore, if droperidol and ondansetron prolong the QT interval, their combination could theoretically increase the risk of cardiac arrhythmia.<sup>11</sup> Interestingly, in the Food and Drug Administration cases of suspected droperidol cardiac toxicity reviewed by Habib *et al.*,<sup>12</sup> one of the most probable cases of arrhythmia

developed in a patient who received droperidol together with dolasetron. Also, the recent report of Nuttall *et al.*<sup>2</sup> described a case of sudden death that occurred few hours after droperidol and ondansetron administration.

The aim of this study was to assess the effects of droperidol and ondansetron alone or in combination on QTc interval duration according to the principles of the E14 guideline.

## Materials and Methods

### Subjects

Healthy adults of both sexes, aged 18–45 yr, were eligible. Subjects were judged healthy on the basis of previous medical history, clinical examination, routine laboratory testing (including plasma potassium, magnesium and calcium, blood cell count, and creatinine and hepatic enzyme levels), and a standard 12-lead electrocardiogram. Only subjects with a normal corrected QT interval (QTc; < 440 ms in males and < 450 ms in females) and resting heart rate between 55 and 70 beats/min were included. All subjects were free of any other medication. The study protocol was approved by the Committee for the Protection of Human Subjects of Saint-Antoine Hospital (Paris, France). All subjects provided written informed consent before entering the study.

### Study Design

This was a prospective, placebo-controlled, double-blind study with four randomized crossover periods where volunteers were given a single dose of droperidol alone, ondansetron alone, droperidol and ondansetron in combination, or a placebo. A washout period greater than 48 h and less than 2 weeks was planned. Randomization was stratified on the sex of the participants. Participants were hospitalized at 7:30 AM at the Clinical Investigation Center (Saint-Antoine Hospital) after an overnight fast. Two intravenous catheters were introduced in forearm veins (one on each side). Obturators were placed in the catheters. Cardiac rhythm and noninvasive blood pressure monitoring were started (Monitor M1204A; Hewlett Packard, Andover, MA). After 30 min of rest in the supine position, drug administration started always following the same protocol. First, 4 mg ondansetron (Zophren®; Glaxo SmithKline, Marly-le-Roi, France) diluted in 28 ml saline or the same volume of saline was administered intravenously using an electrical infusion pump (Pilote C; Fresenius Vial SAS, Brezins, France) programmed to administer the drug over 120 s. The beginning of this infusion defined the time zero in following analysis. Then, 1 mg droperidol (Dropleptan®; OTL Pharma, Cournon, France) diluted in 4 ml saline or the same volume of saline was administered as a 10-s bolus *via*

the same catheter. After the end of each drug (or placebo) infusion, the catheter was rinsed with 5 ml saline. Study drugs were reconstituted by a resident in pharmacy not involved in the care of the participant. A standardized light meal was served 4 h after antiemetic infusions.

### Blood Sampling and Shipping

Blood samples (5 ml) were collected from the opposite forearm catheter before administration of drug study and at 3, 5, 7, 9, 13, 23, 30, 45, 60, 120, 240, 420, and 600 min after administration. Plasma was separated within 30 min and stored at –80°C until analyzed. All samples were shipped to Raymond Poincaré Hospital (Garches, France) for drug assay at the end of the study in a container filled with dry ice.

### Drug Assay and Pharmacokinetic Analysis

Droperidol and ondansetron were quantified in plasma using a liquid chromatography coupled to ion trap mass spectrometry detection with electrospray ionization interface, after basic liquid/liquid extraction using haloperidol and tropisetron as internal standards. Data were collected either in full-scan mass spectrometry mode at a mass-to-charge ratio ( $m/z$ ) of 100–450 or in full-scan tandem mass spectrometry mode, selecting the ion  $m/z$  294 for ondansetron,  $m/z$  285.2 for tropisetron,  $m/z$  380 for droperidol, and  $m/z$  376 for haloperidol. The most intense daughter ions of ondansetron ( $m/z$  212) and droperidol ( $m/z$  194) were used for quantification. Retention times were 2.63 min for ondansetron, 2.50 min for tropisetron, 3.17 min for droperidol, and 4.77 min for haloperidol. Calibration curves were linear for both droperidol and ondansetron in the 0.50- to 500-ng/ml range. The limits of detection and quantification were 0.10 and 0.50 ng/ml, respectively. The intraassay and interassay precisions evaluated at 3, 30, and 300 ng/ml were all less than 6.4%, and the intraassay and interassay accuracies were in the 97.6–101.9% range at 3, 30, and 300 ng/ml.

### Pharmacokinetic Calculations

Pharmacokinetic parameters were calculated by non-compartmental methods using WinNonlin 2.1 (Pharsight, Mountain View, CA). Peak plasma concentration was obtained from observed data. Area under the plasma concentration-*versus*-time curve was calculated with the use of the linear trapezoidal rule. The apparent plasma elimination half-life for droperidol and ondansetron was calculated as  $0.693/k_e$ , where  $k_e$  is the slope of the log (plasma drug concentration)-*versus*-time line after least-squares regression analysis of the terminal portion of this relation.

### Measurement of QT Intervals

At 1-min intervals for the first 15 min after the beginning of drug administration and then after 20, 30, 45, 60, 90, 120, 240, 420, and 600 min, 10-s digital electrocardiograms were recorded using a Cardioplug device (Cardionics Inc, Brussels, Belgium) connected to a personal computer. All electrocardiogram recordings were read by the same blinded investigator (B.C.). The same chest lead with the largest T-wave amplitude was selected for QT interval measurement in a given subject during each study period. QT interval was measured manually directly on the computer screen by changing position of cursors indicating the start and the end of the cardiac interval: RR (interval between two successive R waves) and QT. QT interval was corrected according to the cubic root formula.<sup>13</sup> Baseline QTc was assessed as the mean of three electrocardiographic recordings obtained within 30 min before drug administration. For each electrocardiogram, QTc prolongation was calculated as time-matched placebo and baseline subtracted ( $\Delta\Delta\text{QTcF}$ ). The primary endpoint was the mean maximal  $\Delta\Delta\text{QTcF}$  during the first 30 min after drug administration. In accordance with E14 guideline, we calculated the upper limit of the 95% one-sided confidence interval (CI) of the mean maximal  $\Delta\Delta\text{QTcF}$ . We also analyzed values of QTc interval automatically calculated by the software from an overlapped median beat.

### Statistical Analysis

It was calculated that 15 subjects were necessary to detect a QTc prolongation of at least 15 ms between droperidol or ondansetron alone or in combination compared with placebo, assuming an SD of QTc change of 15 ms (global  $\alpha = 0.05$ ,  $\beta = 0.20$ ). A randomization table, stratified by sex of the participant, was generated by the statistician (Pierre-Yves Boelle, M.D., Ph.D., Assistant Professor, Saint-Antoine Hospital, Department of Public Health, Paris, France) and transmitted to the local pharmacy to prepare drugs in sealed envelopes. The primary endpoint ( $\Delta\Delta\text{QTcF}$ ) was compared among the three groups using a two-way analysis of variance where subjects and treatment effects were considered. In case of significance, *post hoc* analysis used the Tukey test for multiple comparisons. Results are expressed as mean  $\pm$  SD or mean [95% CI]. Analyses were performed using JMP 6.0 software (SAS Institute, Cary, NC). Statistical significance was considered at  $P < 0.05$ .

## Results

### Subject Demography

Sixteen volunteers (eight males and eight females) entered the study. Two participants were excluded after their first study period. One was excluded because of persistent difficulties to obtain a sufficient blood sample.

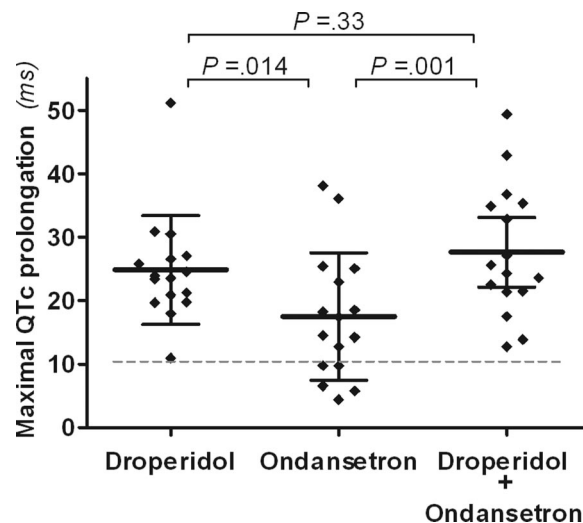


Fig. 1. Mean ( $\pm$ SD) and individual maximal time-matched and placebo-subtracted corrected QT interval prolongation after 1 mg droperidol, 4 mg ondansetron, or their combination in a crossover study of 16 healthy volunteers. *P* values refer to intertreatment comparisons adjusted for the repeated measurement.

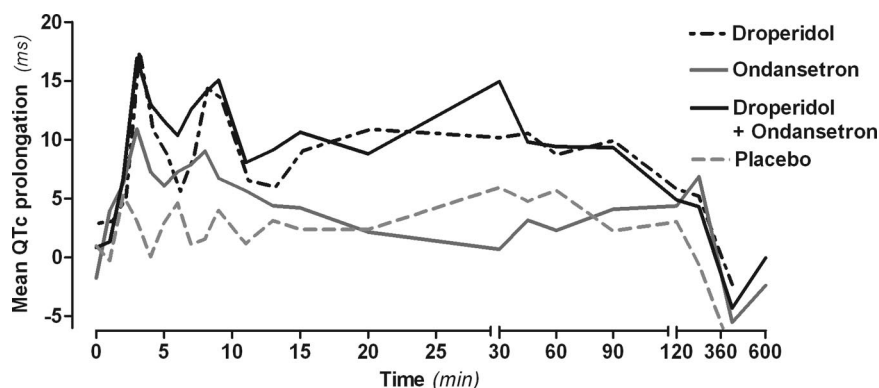
Another subject, a 22-yr-old man, experienced anxiety with abdominal pain 1 h after administration of 1 mg droperidol. He then developed abnormal movements, dyskinesia, and agitation. The symptoms completely resolved within 5 h without treatment. Both participants were replaced. The mean  $\pm$  SD values of the participants' age, height, and body mass index were  $29 \pm 8$  yr,  $171 \pm 9$  cm, and  $24 \pm 3$  kg/m<sup>2</sup>, respectively. The washout period was 5 [2–11] days.

### Electrocardiographic Findings

Compared with placebo, both droperidol and ondansetron significantly prolonged the QTc interval. The upper limits of the 95% one-sided CI of the mean maximal  $\Delta\Delta\text{QTcF}$  were 28.6 and 21.9 ms during droperidol and ondansetron, respectively. The mean maximal  $\Delta\Delta\text{QTcF}$  values were  $25 \pm 8$  and  $17 \pm 10$  ms after droperidol and ondansetron, respectively. The combination of droperidol and ondansetron also significantly increased the mean maximal  $\Delta\Delta\text{QTcF}$  by  $28 \pm 10$  ms. Maximal QTc prolongation was significantly greater in the droperidol and droperidol-ondansetron groups compared with ondansetron alone ( $P = 0.014$  and  $P = 0.001$ , respectively; fig. 1). Maximal QTc prolongation was not different between droperidol and droperidol-ondansetron ( $P = 0.33$ ).

The time courses of mean  $\Delta\Delta\text{QTcF}$  values by treatment are shown in figure 2. There was no significant interaction between time and treatments ( $P = 0.18$ ). However, the duration of significant QTc prolongation was different within groups. Volunteers receiving ondansetron alone prolonged their QT interval until the 4th min and then at the 7th, 8th, and 11th min. During droperidol, QTc significantly differed from zero from the end of

Fig. 2. Time course evolution of mean time-matched and placebo-subtracted corrected QT interval prolongation after 1 mg droperidol, 4 mg ondansetron, their combination, or placebo in a crossover study of 16 healthy volunteers.



infusion to the 20th min, with the exception of the 6th and 13th min. When droperidol was given after ondansetron, QTc remained prolonged until the 30th min.

Compared with placebo, ondansetron induced a transient decrease in heart rate of 6 beats/min at the end of drug infusion. In contrast, droperidol increased heart rate by 6–10 beats/min at the end of the infusion but also between the 6th and 8th min. The combination of antiemetics significantly increased heart rate by 8 beats/min around the 8th min. Neither systolic nor diastolic blood pressure was modified by droperidol and ondansetron over the first 30 min ( $P = 0.69$  and  $P = 0.25$ , respectively).  $\Delta\Delta\text{QTcF}$  prolongation was not statistically different between males and females, and there was no significant period order effect.

Analysis was performed again using the Bazett QT correction formula. Results were similar, but the extent of the  $\Delta\Delta\text{QTc}$  prolongation increased with both drugs. Maximal QTc prolongation was  $42 \pm 21$  ms with droperidol,  $24 \pm 12$  ms with ondansetron, and  $43 \pm 19$  ms after droperidol plus ondansetron.

Automatic QTc values gave consistent results with  $\Delta\Delta\text{QTcF}$  of  $29 \pm 17$ ,  $15 \pm 6$ , and  $25 \pm 14$  ms for droperidol, ondansetron, and droperidol plus ondansetron, respectively. QTc prolongation induced by droperidol alone was statistically different from that induced by ondansetron alone ( $P = 0.005$ ) but not significantly different from QTc prolongation observed during the combination of droperidol and ondansetron ( $P = 0.37$ ).

### Categorical (Outlier) Analysis of QTc Effects of Droperidol and Ondansetron

During the first 30 min, maximal QTc prolongation from baseline was greater than 30 ms in 9 of the 16 participants, 5 during droperidol, 2 during ondansetron, 7 during the combination, and 1 after placebo ( $\chi^2 = 8.3$ ,  $P = 0.04$ ). None of the participants had QTc prolongation greater than 60 ms or over 500 ms. No ventricular arrhythmia was noted during the study.

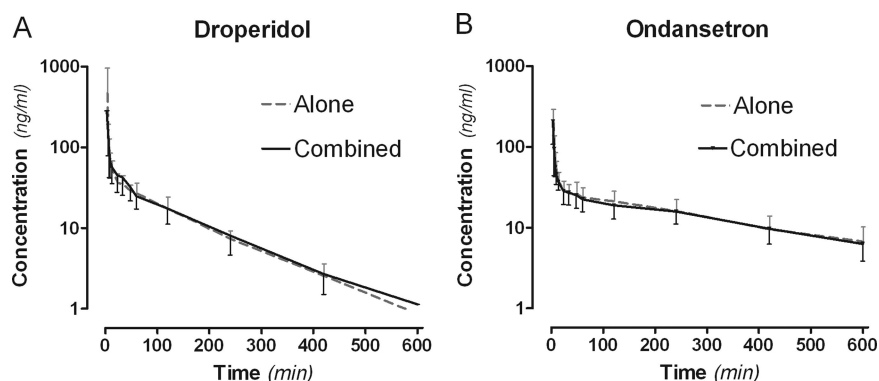
### Pharmacokinetics of Droperidol and Ondansetron

The time courses of droperidol and ondansetron plasma concentrations are shown in figure 3. For all participants at each period, the first blood sample before drug administration was below the detection limit for both droperidol and ondansetron. Pharmacokinetic parameters are shown in table 1. The ratio of areas under the concentration-time curves (combination/alone) after log transformation were 0.996 [90% CI, 0.86–1.16] and 0.975 [90% CI, 0.88–1.08] for droperidol and ondansetron, respectively. This indicates that there was no pharmacokinetic interaction between the two drugs.

### Pharmacokinetic/Pharmacodynamic Analysis

We analyzed data using samples where drug concentrations were greater than 50 ng/ml ( $n = 64$  for droperidol and  $n = 52$  for ondansetron, 31% and 25% of all samples, respectively). There was a significant

Fig. 3. Plasma concentrations time course profiles after 1 mg droperidol (A) and 4 mg ondansetron (B) when these drugs were administered either alone (dashed curves) or in combination (plain curves) in a crossover study of 16 healthy volunteers.



**Table 1. Pharmacokinetic Profiles of Droperidol and Ondansetron Administered Alone or in Combination**

	Droperidol		Ondansetron	
	Alone	With Ondansetron	Alone	With Droperidol
$C_{\max}$ , ng/ml	143 [111–896]	225 [130–378]	175 [116–259]	216 [131–264]
Elimination $t_{1/2}$ , h	1.90 [1.46–2.12]	1.74 [1.49–1.94]	4.70 [3.85–5.54]	4.57 [4.09–5.28]
$AUC_{0-\infty}$ , ng · h · ml <sup>-1</sup>	110 [96–127]	114 [90–127]	175 [127–253]	197 [133–232]
Clearance, ml/min	151 [131–174]	146 [131–186]	381 [265–529]	339 [287–504]

Results are shown as median [interquartile range]. All comparisons of drug alone vs. combination were not statistically significant.

$AUC_{0-\infty}$  = total area under the plasma concentration–time curve;  $C_{\max}$  = peak concentration in the plasma;  $t_{1/2}$  = half-life.

relation between droperidol concentration and QTc interval prolongation ( $r = 0.34$ ,  $P = 0.005$ ; fig. 4A). In contrast, the relation between QTc prolongation and ondansetron concentrations did not reach statistical significance ( $r = 0.16$ ,  $P = 0.26$ ; fig. 4B). During the combination period, in univariate analysis, droperidol but not ondansetron concentrations were statistically correlated with QTc prolongation ( $P = 0.043$  and  $P = 0.19$ , respectively). However, in multivariable linear regression analysis, between QTc prolongation and drug concentration, a significant relation was not found ( $P = 0.16$  and  $P = 0.64$  for droperidol and ondansetron, respectively).

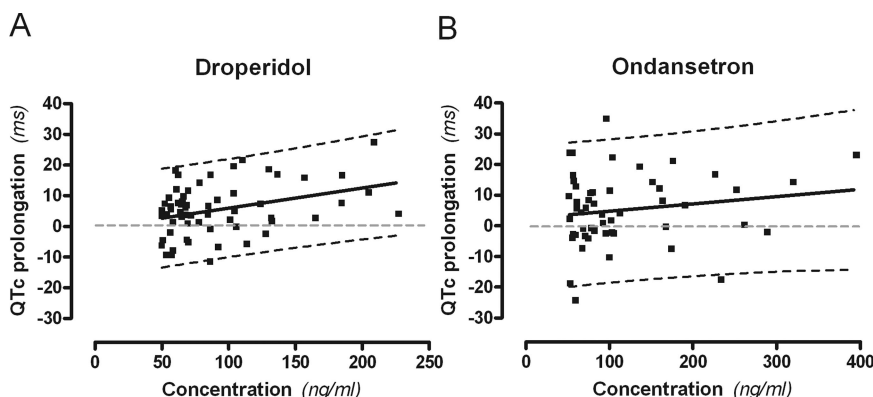
## Discussion

We observed significant QTc interval prolongation during droperidol and ondansetron administration at low antiemetic doses. The effect of droperidol was significantly greater than that of ondansetron. The pharmacodynamic effect of the combination of these drugs was not additive and was not different from that induced by droperidol alone. There was no pharmacokinetic interaction between these antiemetics.

This study is the first report showing significant QTc prolongation after low doses of droperidol and ondansetron measured under conditions recommended by the International Conference on Harmonisation E14 guideline on the evaluation of proarrhythmic risk for noncardiac drugs. Previous clinical studies gave inconsistent results. White *et al.*<sup>7</sup> found a 22-ms QT prolongation

with 1.25 mg droperidol. This QT prolongation was not statistically different from the 12-ms QTc lengthening observed in the placebo group. However, this study was only powered to detect a QTc change of 15% (*i.e.*, approximately 60 ms) and was performed after induction of anesthesia, a phase during which repolarization is known to be unstable. The most remarkable feature of this observation is that two patients experienced QTc lengthening of 120 and 133 ms after receiving 0.625 and 1.25 mg droperidol, respectively. In a study that was not placebo controlled, we found a 17-ms QT interval prolongation with 0.75 mg droperidol and a 20-ms lengthening after 4 mg ondansetron; however, this study was not designed to compare the magnitude of QT prolongation with both drugs.<sup>8</sup> Although not designed for the assessment of QTc change, another report, by Chan *et al.*,<sup>10</sup> found significant QT prolongation after droperidol but also ondansetron. Finally, the extent of maximal droperidol and ondansetron-induced QTc prolongation, *i.e.*, 24 and 17 ms, in the current study is consistent with these previous reports.

Our study is the first one designed to compare droperidol and ondansetron-induced QT prolongation. Our finding of greater QTc prolongation with droperidol in comparison with ondansetron was confirmed by categorical analysis of patients who experienced QTc lengthening greater than 30 ms. This event occurred more frequently during droperidol than during ondansetron. However, this result is possibly explained by the drug administration modalities that we chose. Ondansetron was administered by slow intravenous infusion, in accordance with



**Fig. 4.** Concentration–effects relations on corrected QT interval prolongation of 1 mg droperidol (A) and 4 mg ondansetron (B) administered alone in a crossover study of 16 healthy volunteers. Only post-distribution concentrations are shown. The linear regression was significant with droperidol ( $r = 0.34$ ,  $P = 0.005$ ) but not with ondansetron ( $r = 0.16$ ,  $P = 0.26$ ). Continuous lines represent the linear regression with the 95% prediction band.

the Summary of Product Characteristics,<sup>§§</sup> whereas droperidol was administered as a rapid intravenous bolus. This resulted in greater plasma concentrations for droperidol, which may have induced greater QT prolongation. We also cannot exclude that ondansetron-induced QT prolongation would be of greater extent if administered as a rapid intravenous bolus, as is often done in clinical practice. However, in experimental studies, the rate of infusion of QT-prolonging drugs does not change the extent of maximal QT prolongation.<sup>14</sup> Nevertheless, experimental data support our clinical observation and indicate different inhibitory effects of droperidol and ondansetron on HERG channels. Drolet *et al.*<sup>15</sup> calculated that 32 nM droperidol (approximately 12 ng/ml) inhibits 50% of the current carried by HERG channels. Kuryshv *et al.*<sup>4</sup> found that the most potent inhibitor of this current among four 5-hydroxytryptamine type 3 receptor antagonists assessed was ondansetron, with an IC<sub>50</sub> of 808 nM (approximately 236 ng/ml) on HERG channel. Therefore, the ratio of inhibitory concentration, equal to 20, confirms the much more potent inhibitory effect of droperidol on the principal cardiac channel responsible for torsade de pointes and sudden death. Even if taking into account the dose of ondansetron that is four times the dose of droperidol, the expected effect would still be favorable to ondansetron. In the current study, the maximal observed plasma concentrations of drugs administered alone were approximately 400 nM for droperidol and 600 nM for ondansetron. These maximal concentrations, much higher than HERG IC<sub>50</sub> of droperidol, seem to be one major argument for the greater QTc prolongation observed with droperidol at usual doses. Moreover, at the 10th minute, plasma concentration decreased to approximately 150 nM, a concentration that still blocks HERG channel with droperidol but weakly with ondansetron. However, this calculation does not take into account the protein binding of both antiemetics (approximately 70%; data of the manufacturers) given that experimental models use unbound drugs. Therefore, for ondansetron, the unbound drug that can interact with HERG channel after the 10th minute may be very low, explaining the lack of prolonged QTc lengthening. Finally, although extrapolations from experimental data must be prudent, they are a possible explanation for the lack of relation between ondansetron and QTc prolongation.

The current study did not find an additive effect of droperidol and ondansetron on QTc prolongation. In fact, the addition of droperidol to ondansetron did not increase the extent of maximal QTc prolongation. However, the combination induced greater QTc lengthening than ondansetron administered alone. We cannot ex-

clude that concomitant administration of drugs would result in a greater effect. A previous study did not find additive QTc prolongation between the droperidol and ondansetron.<sup>10</sup> However, this study was designed to assess the efficacy on postoperative nausea and vomiting of antiemetic combination but not its electrocardiographic effects.<sup>10</sup> Moreover, in this study, electrocardiograms were only obtained 5 min after drug administration, precluding the assessment of the maximal QTc prolongation, which is known to be the better surrogate of drug-induced arrhythmia.<sup>10</sup> The lack of additive effect of the two drugs on QTc interval may also be explained by experimental data. In fact, the greater droperidol blocking activity of HERG channel explains the lack of supplemental inhibition of HERG with ondansetron if we hypothesize a competitive interaction. However, the two cases of possible arrhythmic event after combining droperidol and setrons should prompt greater caution when QT-prolonging agents are combined.<sup>2,12</sup>

Results of pharmacokinetic analysis are consistent with previous reports, confirming the relative short half-life of both drugs.<sup>16-18</sup> The current study also assessed, for the first time, the possibility of a pharmacokinetic interaction between droperidol and ondansetron using a sensitive liquid chromatography assay coupled with mass spectrometry. None of the principal pharmacokinetic parameters were significantly altered by the administration of the other antiemetic.

#### *Evaluation of Proarrhythmic Risk*

Recently, Nuttall *et al.*<sup>2</sup> assessed the impact of the black box warning on the incidence of QT prolongation, torsade de pointes, and sudden death related to droperidol. Although their article did not take into account a possible case of sudden death occurring after droperidol exposure, the risk of arrhythmia was estimated to be less than 3.6 per 10,000. Although the acceptability of this level of risk has been debated elsewhere,<sup>19</sup> the extrapolation of our data to clinical practice is not easy. We used guidelines accepted by regulatory agencies to assess both droperidol's and ondansetron's risk of proarrhythmia. The threshold of a mean maximal QTc prolongation of approximately 5 ms with an upper limit of the one-sided 95% CI of the mean below 10 ms was exceeded for both antiemetics. Therefore, if one considers that these thresholds are applicable to drugs administered as an intravenous bolus with transient QT prolongation, we cannot consider the proarrhythmic risk to be nonexistent. The current observation may have potential consequences: The warning regarding droperidol may be reinforced, and a warning on ondansetron may need to be added.

#### *Consequences for Drug Administration*

In contrast with our previous report in patients, none of the participants in this study had QTc greater than 500 ms

§§ Zofran [package insert]. Research Triangle Park, North Carolina, GlaxoSmithKline, 2006. Available at: [http://us.gsk.com/products/assets/us\\_zofran\\_tablets.pdf](http://us.gsk.com/products/assets/us_zofran_tablets.pdf). Accessed March 11, 2008.

after drug administration. This threshold is known to increase the individual risk of torsade de pointes.<sup>20</sup> However, one should not consider that because no QTc prolongation of greater than 500 ms was observed in healthy volunteers in the current study, there is no potential for proarrhythmia in patients receiving droperidol or ondansetron for postoperative nausea and vomiting. Indeed, in the postoperative period, the repolarization reserve is decreased as reflected by the high incidence of prolonged QT interval.<sup>13</sup> The decrease in repolarization reserve, in particular induced by halogenated anesthetics, increases the effects of QT-prolonging drugs.<sup>21</sup> Moreover, droperidol has been shown to increase the repolarizing effects of sotalol, another delayed rectifier potassium current blocker, in dogs.<sup>22</sup> In healthy volunteers, where QTc is normal before drug administration, values of QTc greater than 500 ms are only caused by the most toxic drugs or by latent long-QT syndrome with normal basal QTc values. However, our results suggest that droperidol and ondansetron should be administered cautiously when QT interval is previously prolonged, *i.e.*, in the case of congenital or acquired prolonged QT interval. This could be the case when drugs are administered as rescue treatment in patients with possible reduced repolarization reserve resulting, *e.g.*, from the use of volatile anesthetics or hypothermia.

In conclusion, droperidol and ondansetron induce QT interval prolongation at low antiemetic doses. Although ondansetron seems to bear a less toxic potential than droperidol, both drugs should be cautiously administered in patients with prolonged QT interval. Their combination does not seem to increase the proarrhythmic risk of droperidol.

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