Anesthesiology 2005; 102:1094–1100

Prolongation of QTc Interval after Postoperative Nausea and Vomiting Treatment by Droperidol or Ondansetron

Beny Charbit, M.D., Pierre Albaladejo, M.D., Ph.D.,† Christian Funck-Brentano, M.D., Ph.D.,‡ Mathieu Legrand, M.D.,§ Emmanuel Samain, M.D., Ph.D.,‖ Jean Marty, M.D., Ph.D.#*

CME This article and its accompanying editorial have been selected for the *Anesthesiology* CME Program. After reading both articles, go to http://www.asahq.org/journal-cme to take the test and apply for Category 1 credit. Complete instructions may be found in the CME section at the back of this issue.

Background: **At dosages above 0.1 mg/kg, droperidol induces a dose-dependent QTc interval prolongation. Although subject to controversy, low-dose droperidol has recently been suspected to induce cardiac arrhythmias. Hence, 5-hydroxytryptamine type 3 antagonists have become the first-line drug for management of postoperative nausea and vomiting. These drugs are also known to prolong the QTc interval at high dosages. This study describes QTc interval changes associated with postoperative nausea and vomiting treatment by droperidol or ondansetron at low doses.**

Methods: **Eighty-five patients with postoperative nausea and vomiting were included in this prospective, single-blind study. Patients received either 0.75 mg intravenous droperidol (n = 43) or 4 mg intravenous ondansetron (n = 42). Electrocardiographic recordings were obtained before administration of antiemetic drug and then 1, 2, 3, 5, 10, and 15 min after. Electrocardiographic monitoring was maintained for 3 h in eight patients in each group.**

Results: **The QTc interval was prolonged (> 450 ms in men, > 470 ms in women) in 21% of the patients before antiemetic drug administration. This was significantly correlated with lower body temperature and longer duration of anesthesia. Compared with predrug QTc measurement, both antiemetics were associated with a significant QTc interval prolongation ($P < 0.0001$). The mean maximal QTc interval prolongation was 17 ± 9 ms after droperidol occurring at the second minute and 20 ± 13 ms after ondansetron at the third minute (both $P < 0.0001$). Compared with predrug measurement, the QTc interval was significantly lower after the 90th minute in both groups.**

Conclusions: **Droperidol and ondansetron induced similar clinically relevant QTc interval prolongations. When used in treatment of postoperative nausea and vomiting, a situation where prolongation of the QTc interval seems to occur, the safety of 5-hydroxytryptamine type 3 antagonists may not be superior to that of low-dose droperidol.**

This article is accompanied by an Editorial View. Please see: Scuderi PE: You (still) can't disprove the existence of dragons. ANESTHESIOLOGY 2005; 102:1081–2.

DRUG-INDUCED prolongation of the QTc interval has become the first cause of drug withdrawal or use restriction in the past years because of the potential risk of life-threatening polymorphic ventricular tachycardia, torsade de pointes.[1] Several drugs used during general anesthesia induce lengthening of cardiac repolarization (thiopental, suxamethonium, and all volatile anesthetics).[2–4]

The butyrophenone droperidol and all selective 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists are routinely used to prevent or treat postoperative nausea and vomiting (PONV).[5] These drugs are known to prolong the QTc interval at high dosages.[6–8] After reports of fatal arrhythmias associated with droperidol use, in particular in high doses used in psychiatric patients, the US Food and Drug Administration warned healthcare providers about droperidol use even in low doses in December 2001. Since this warning, there has been controversy about droperidol use even at lower dosages.[9–13] This antiemetic drug is known to induce dose-dependent QTc interval lengthening at doses above 0.1 mg/kg.[8] *In vitro*, droperidol induces potassium channel blockade.[14] At the low doses recommended in the prevention or treatment of PONV, evidence of droperidol-induced cardiac adverse events, in particular torsades de pointes, is lacking.[15]

Hence, 5-HT_3 antagonists have become the first-line treatment both for prevention and treatment of PONV.[5] However, 5-HT_3 antagonists (ondansetron, granisetron, and dolasetron) are listed among QT interval–prolonging drugs with possible risk of torsade de pointes.** Moreover, several cases of cardiac dysrhythmias after administration of 5-HT_3 antagonists have been reported.[16,17]

The lack of reliable QTc data in patients treated with low doses of droperidol or 5-HT_3 antagonists contributes to the controversy about their safe use in the perioperative period. Therefore, the aim of this study was to describe QTc interval changes associated with administration of low-dose droperidol or ondansetron to treat PONV.

* Assistant Professor of Anesthesiology, Department of Anesthesiology and Intensive Care, Beaujon University Hospital, Assistance Publique-Hôpitaux de Paris. Division of Clinical Pharmacology, Saint-Antoine University Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France. † Staff Anesthesiologist, § Resident in Anesthesiology, # Professor of Anesthesiology and Head of Department, Department of Anesthesiology and Intensive Care, Beaujon University Hospital, Assistance Publique-Hôpitaux de Paris. ‡ Professor of Pharmacology, Division of Clinical Pharmacology, Saint-Antoine University Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France. ‖ Professor of Anesthesiology and Head of Department, Department of Anesthesiology and Intensive Care, Jean Minjoz University Hospital, Besançon, France.

Received from the Department of Anesthesiology and Intensive Care, Beaujon University Hospital, Assistance Publique-Hôpitaux de Paris, University Xavier Bichat Paris 7, Clichy, France. Submitted for publication July 7, 2004. Accepted for publication November 23, 2004. Support was provided solely from institutional and/or departmental sources. Drs. Charbit and Albaladejo contributed equally to this work.

Address reprint requests to Dr. Charbit: Division of Clinical Pharmacology, St-Antoine University Hospital, 184 rue du faubourg Saint-Antoine, 75571 Paris Cedex 12, France. Address electronic mail to: beny.charbit@sat.aphp.fr.

** Available at: http://www.torsades.org. Accessed December 10, 2004.

Table 1. Demographic and Clinical Characteristics of Patients Treated with Droperidol or Ondansetron

Characteristic	Droperidol (n = 43)	Ondansetron (n = 42)	*P* Value
Mean age, yr	46 ± 16	44 ± 16	0.6
Sex ratio, n, M/F	17/26	17/25	0.9
Operative procedure, n			0.3
Vascular	3	4	
Neurosurgery	6	9	
Ear, throat, and nose	8	8	
Orthopedics	10	2	
Gynecology	6	7	
Other	10	12	
Duration of anesthesia, min	187 ± 114	199 ± 114	0.7
Delay between end of anesthesia and PONV, min	67 ± 63	68 ± 58	0.9
Temperature, °C	36.3 ± 0.8	36.2 ± 0.7	0.6
Procedure during general anesthesia, %	88	83	0.7

PONV = postoperative nausea and vomiting.

Materials and Methods

This study was approved by the ethics committee of Paris Cochin (Paris, France). Each patient gave informed consent to be included in this observational study. Patients with nausea or vomiting in the recovery room were consecutively included. Exclusion criteria were prophylactic antiemetic drug administration during the operative period, a known prolonged QTc interval, a decompensated cardiomyopathy, cardiac arrhythmia, or bundle-branch block.

Either 0.75 mg droperidol (Droleptan®; OTL Pharma, Cournon, France) or 4 mg ondansetron (Zophren®; Glaxo SmithKline, Marly-le-Roi, France) was administered as an intravenous bolus when a patient experienced PONV in the recovery room according to the attending anesthesiologist. The study was nonrandomized, but electrocardiographic evaluations were made without any knowledge of the different therapeutic interventions. Standard postoperative monitoring, including electrocardioscopy, blood pressure monitoring, and pulse oximetry, was routinely used during the postoperative room stay. Tympanic temperature was obtained with a digital thermometer (First temp genius; Sherwood Medical, Crawley, United Kingdom). Apart from serial electrocardiographic recordings, care of the patients was not modified by this study.

Electrocardiographic Recordings

Unfiltered 12-lead electrocardiograms were obtained from all subjects immediately before administration of antiemetic drug (baseline) and 1, 2, 3, 5, 10, and 15 min after intravenous injection. In eight patients in both groups, additional electrocardiographic recordings were performed 30, 45, 60, 90, 120, and 180 min after antiemetic administration. Electrocardiograms were recorded at a paper speed of 50 mm/s and an amplitude of 2 cm/mV with a Pagewriter M1770 device (Hewlett Packard, Andover, MA). Reading and analysis of the electrocardiographic tracings were performed after completion of the study by the same investigator (B. C.) who was blinded to the antiemetic drug received. QT and R-R intervals were measured manually by averaging five successive cardiac beats and using a digitizing pad (SummaSketch II Professional; Summagraphics, Seymour, CN) connected to a microcomputer. For each patient, the chest lead with the largest T-wave amplitude at baseline was selected for all QT interval measurements. The QT interval was measured as described previously[18] and corrected for heart rate (QTc) according to the formula of Bazett ($QTc = QT/\sqrt{R\text{-}R}$).

To assess spontaneous evolution of QTc interval duration in the postoperative period, serial electrocardiograms were performed in 10 additional patients 1 h after arrival in the recovery room and then 1, 2, 3, 5, 10, 15, 30, and 60 min after the first electrocardiographic recording.

Statistical Analysis

Results are expressed as mean ± SD unless otherwise specified. To detect a QTc change from baseline greater

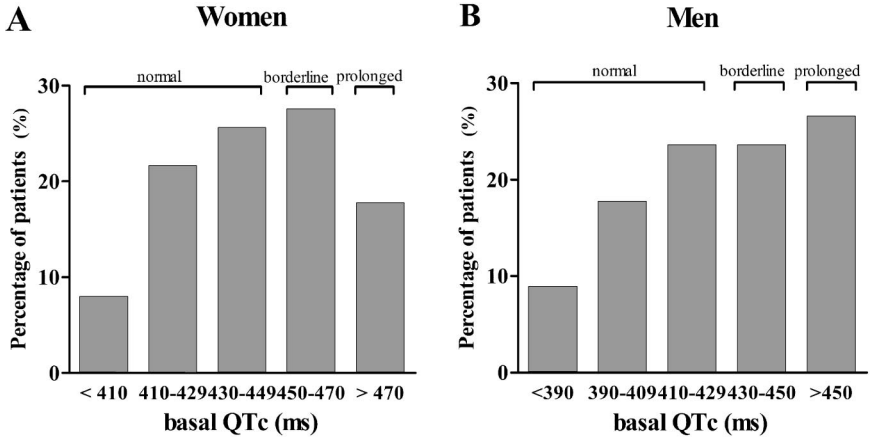

Fig. 1. Distribution of QTc interval duration in women (*A*) and men (*B*) with postoperative nausea and vomiting before antiemetic drug administration. Normal, borderline, and prolonged QTc intervals according to the Committee for Proprietary Medicinal Products definition for each sex (see text).

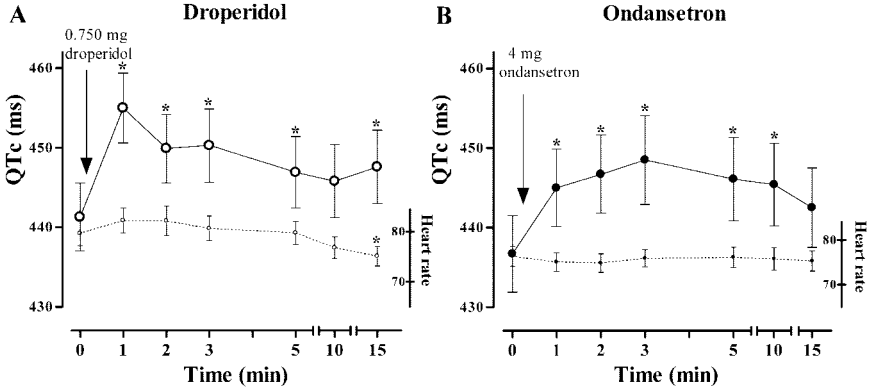

Fig. 2. Mean QTc interval duration (± SE; milliseconds; *left axis*) and heart rate (± SE; beats/min; *right axis*, *dotted line*) *versus* time interval (minutes) between injection of antiemetic and QTc interval measurement. (*A*) Droperidol, 0.75 mg, or (*B*) ondansetron, 4 mg, administered in patients with postoperative nausea and vomiting. In both groups, analysis of variance for repeated measurement was significant ($P < 0.001$). * $P < 0.05$ *versus* baseline in the same treatment group.

than 5 ms with α and β risks of 0.05 and 0.20, respectively, and assuming an SD of QTc change of 10 ms, a minimum of 34 subjects were needed in each antiemetic group. Comparison of QTc intervals at different times was performed by one-way repeated-measures analysis of variance and, if significant, *post hoc* analyses used the Dunnett test, using baseline as the reference value for normally distributed data, and the Wilcoxon test elsewhere. Maximal QTc interval change and its time of occurrence were determined manually by examination of individual data until the fifth minute after drug administration. The confidence interval of proportion was calculated using the Wilson method. Simple regression analyses were performed by standard methods. Multiple regression analysis was performed to assess the influence of covariates. All data passed the Kolmogorov-Smirnov test for gaussian distribution criteria. Analyses were performed using StatView 6.0 software (SAS institute, Cary, NC). Statistical significance was considered at $P < 0.05$.

Results

Eighty-five patients with PONV were consecutively included in the study. Among them, 43 received droperidol, and 42 received ondansetron. None were taking QT interval–prolonging drugs associated with a demonstrated risk of torsade de pointes before anesthesia. Demographic and clinical characteristics are reported in table 1.

Electrocardiographic Recordings before Drug Administration

The mean QTc interval was 439 ± 29 ms before antiemetic drug administration. According to sex-related thresholds†† (QTc > 450 ms in men, > 470 ms in women; fig. 1), a prolonged QTc interval was found in 18 of the 85 patients (9 men, 9 women), representing a global percentage of 21% (95% confidence interval, 14–31%).

In patients who underwent surgery during general anesthesia (n = 73), the basal QTc interval value was inversely correlated with body temperature ($r = -0.500$, $P < 0.001$) and positively correlated with duration of anesthesia ($r = 0.341$, $P = 0.003$). Because a correlation was found between these two parameters, they were tested in multivariate regression analysis. Global prediction of a model including temperature and duration of anesthesia as covariate was increased ($r = 0.547$, $P < 0.001$), with both temperature and duration of anesthesia being significant.

The incidence of prolonged QTc interval was similar in patients who later received droperidol (10 of 43) or ondansetron (8 of 42). The baseline QTc interval was slightly but not significantly higher in patients who later received droperidol (droperidol: 441 ± 28 ms, ondansetron: 437 ± 31 ms; $P = 0.5$). Heart rate before antiemetic administration did not differ significantly between the groups (droperidol: 80 ± 16 beats/min, ondansetron: 76 ± 14 beats/min; $P = 0.3$).

Electrocardiographic Recordings after Antiemetic Drug Administration

Mean QTc interval measurements over time are shown in figure 2 after droperidol and ondansetron administration. In both groups, we observed significant QTc changes during the 15 min after antiemetic drug administration ($P < 0.0001$). As compared with baseline values, the QTc interval was significantly increased at all measured times except for the 10th minute after administration of droperidol and the 15th minute after ondansetron. Maximal QTc interval lengthening was observed at 2 and 3 min after administration of droperidol and ondansetron, respectively. The mean maximal QTc interval duration until the fifth minute was significantly increased from baseline in both groups ($P < 0.0001$; fig. 3). Maximal QTc lengthening was 17 ± 9 ms after droperidol and 20 ± 13 ms after ondansetron (both $P <$

†† Committee for Proprietary Medicinal Products: The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products. The European Agency for the Evaluation of Medicinal Products. Available at: http://www.emea.eu.int/pdfs/human/swp/098696en.pdf. Accessed December 10, 2004.

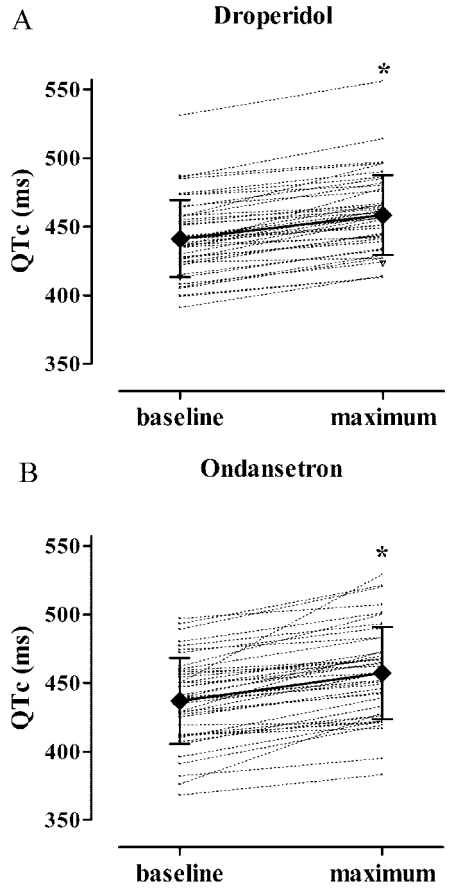

Fig. 3. Individual QTc interval values (milliseconds) at baseline and maximal value until the fifth minute after 0.75 mg droperidol (*A*) and 4 mg ondansetron (*B*). *Thick line* represents mean (± SD). Mean maximal QTc increase was 17 ± 9 ms after droperidol (*A*) and 20 ± 13 ms after ondansetron (*B*). * $P < 0.05$ *versus* baseline.

0.0001). Heart rate remained stable over time in both study groups (the only significant change compared with baseline was observed at 15 min in the droperidol group; fig. 2). QTc interval changes were similar when using the cubic root Fridericia correction formula.

To examine whether the increase in QTc interval duration after antiemetic administration was influenced by baseline QTc value, we plotted maximal QTc as a function of basal QTc. The slope of the linear regression ($r = 0.93$, $P < 0.0001$) was 0.97, with a 95% confidence interval of 0.89–1.05, indicating that the extent of QTc increase did not depend on its initial value.[19]

Prolonged Electrocardiographic Monitoring

Figure 4, which represents 3-h follow-up QTc measurement after droperidol or ondansetron, shows a significant decrease of QTc interval duration over time. From the 90th to the 180th minute after antiemetic administration, the QTc interval was significantly lower compared with baseline in both groups ($P < 0.05$).

Although the study was not designed to compare QTc interval durations during droperidol and ondansetron, there was no statistically significant difference between QTc interval durations at any time among patients who received droperidol or ondansetron.

Categorical Analysis

In 8 patients, the QTc interval increase from baseline was greater than 30 ms: 2 during droperidol (39 and 43 ms) and 6 during ondansetron (31, 31, 38, 44, 52, and 69 ms). Among them, 1 patient experienced QTc lengthening greater than 60 ms after ondansetron administration. A QTc interval greater than 500 ms was recorded in 10 patients (4 during droperidol and 6 during ondansetron) within the 15 min after drug administration. Representative electrocardiograms of two patients, one after each antiemetic, reaching QTc values greater than 500 ms are shown in figure 5.

Spontaneous Variability of QTc Interval Duration

In patients not receiving antiemetic drug, we did not observe a significant change in QTc interval duration over the 15-min period after the first electrocardiogram. The maximal QTc increase between the first and fifth minutes of recordings was 2 ± 2 ms as compared with baseline ($P = 0.03$). At 30 and 60 min, QTc significantly decreased as compared with baseline ($P < 0.05$; fig. 6).

No ventricular arrhythmia was noted during the study period. In one woman, supraventricular tachycardia occurred 10 min after ondansetron administration. It was well tolerated and resolved spontaneously in approximately 5 min.

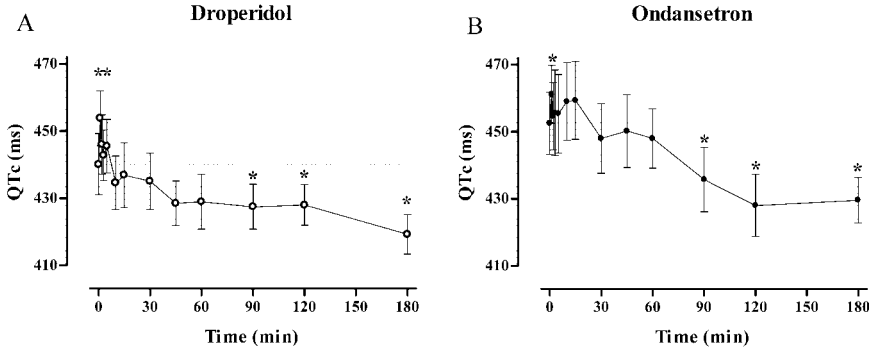

Fig. 4. Three-hour electrocardiographic follow-up after 0.75 mg droperidol (*A*) or 4 mg ondansetron (*B*) for eight patients in each group. Mean QTc interval duration (± SE; milliseconds) *versus* time interval (minutes) between injection of antiemetic and QTc interval measurement. *Dotted line* represents initial QTc value. * $P < 0.05$ *versus* baseline.

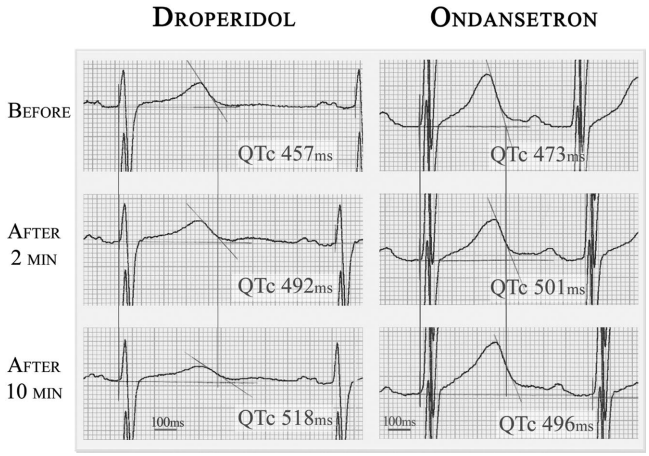

Fig. 5. Electrocardiographic recordings in two representative subjects who received 0.75 mg droperidol (female patient, *left*) or 4 mg of ondansetron (male patient, *right*) to treat postoperative nausea and vomiting. Upper electrocardiograms were obtained immediately before antiemetic administration, and the recordings performed after 2 and 10 min are shown below. The same chest lead is shown for each patient. Note the flattened T wave occurring after droperidol and changes in T-wave morphology after ondansetron. Electrocardiograms were recorded at a paper speed of 50 mm/s and an amplitude of 20 mm/mV.

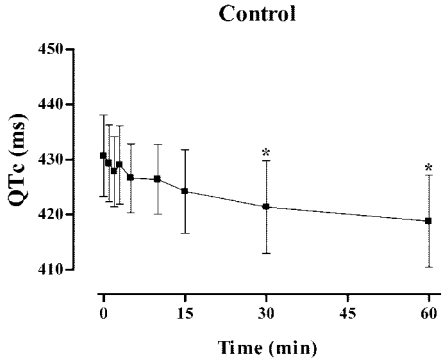

Fig. 6. Mean QTc duration (± SE; milliseconds) *versus* time in the postoperative period in 10 patients without antiemetic administration. The first electrocardiogram was obtained 1 h after the end of general anesthesia. * $P < 0.05$ *versus* baseline.

Discussion

We have observed a high prevalence of QTc interval prolongation in patients with PONV before antiemetic drug administration. In these patients, we found significant changes in QTc interval duration after administration of both droperidol and ondansetron.

QTc Interval Prolongation in the Recovery Room

According to Committee for Proprietary Medicinal Products (London, United Kingdom), a QTc interval corrected for heart rate above 450 ms in men and 470 ms in women is considered to be prolonged. We have observed a high prevalence of prolonged QTc intervals in our patients before treatment of PONV. Although we do not have preoperative electrocardiograms for the majority of our patients, our high prevalence of long QTc intervals does not reflect the expected 1 in 1,000 prevalence of long QT syndrome.[20] Therefore, a perioperative increase in duration of ventricular repolarization seems the most probable explanation. We have found significant correlations between body temperature, duration of general anesthesia, and baseline QTc interval duration. Hypothermia is a known factor of cardiac repolarization prolongation.[21] During anesthesia, many drugs, such as propofol,[22] thiopental,[23] halogenated agents,[24] or opioids,[25] interact with potassium channels involved in the repolarization process. Therefore, the duration of anesthesia is possibly an indirect index of impregnation of halogenated anesthetics and opioids. Furthermore, as found in the 16 patients in whom electrocardiograms were obtained up to 3 h after antiemetic drug administration and in the 10 patients who did not receive any antiemetic and had electrocardiographic recordings up to 60 min 1 h after their arrival in the recovery room, the QTc interval seems to decrease during the postoperative period. Other factors, such as pain or stress-induced sympathetic stimulation or perioperative electrolytes changes, in particular potassium and magnesium, may possibly be underestimated.[20] Moreover, although vomiting is not a known factor of QTc interval prolongation, we can hypothesize that this particular situation may also have effects on repolarization as a consequence of sympathovagal stimulation during vomiting efforts.

Because a decrease in repolarization reserve, as reflected by basal QTc interval lengthening, seems to occur in the postoperative period, a QT interval–prolonging drug should be prescribed with great caution.

Evaluation of Proarrhythmic Potential of Droperidol and Ondansetron

International guidelines have been proposed to assess the proarrhythmic potential for nonantiarrhythmic drugs.‡‡ Recommendations are to combine *in vitro* studies, *in vivo* studies, and postmarketing drug surveillance. *In vitro* studies usually assess drugs effects on ionic currents involved in cardiac repolarization. These studies have been performed both with droperidol[14] and with 5-HT_3 antagonists.[6,26] Droperidol has been found to induce a potent block of the rapid component of the delayed rectifier potassium current (I_{Kr}).[14] I_{Kr} is the main repolarizing channel in the human heart, which is encoded by the human ether-a-go-go–related gene HERG. Mutations of this gene are involved in congenital long QT syndrome. Moreover, all drugs inducing torsades de pointes block I_{Kr} current. All 5-HT_3 antagonists also

‡‡ S7B Revised: The Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals. E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. Available at: http://www.ich.org. Accessed, December 10, 2004.

block the I_{Kr} current but also Na^+ channels, resulting in lengthening of both depolarization and repolarization.[26]

In vivo, human studies have also been conducted with both droperidol and ondansetron, but only at high dosages. QTc interval increases of 37 ms have been reported after an intravenous bolus of 0.1 mg/kg droperidol in patients under general anesthesia.[8] In healthy volunteers, 32 mg ondansetron administered intravenously was found to prolong the QTc interval, but without assessment of initial QTc changes.[6,7] No study on the effects on QTc interval duration has been published with both of these drugs when used in low doses in recovery patients.

We have observed significant QTc interval changes after administration of both antiemetics. Although for obvious ethical reasons our study did not have a placebo control group, many arguments support a relation between QTc interval prolongation and drug administration. First, the QTc interval was increased in almost all subjects with QTc changes of much greater amplitude compared with patients who did not receive any antiemetic. Second, the maximal observed effect was consistent with the pharmacokinetic profiles of both drugs with early peak plasma concentration after intravenous bolus. This is consistent with the study of Lischke *et al.*,[8] who found maximal QTc interval prolongation occurring in the first minute after intravenous droperidol administration. Furthermore, observed maximal QTc interval prolongation after droperidol administration is consistent with recently published extrapolation of available QTc data,[8] concluding that 0.625 mg droperidol would produce a QTc interval prolongation of 9 ± 3 ms in patient weighing 100 kg.[27] However, our study has some limitations. First, it describes two different therapeutic interventions without randomization, but electrocardiographic analyses were blinded to the administered antiemetic. Moreover, both groups had similar baseline clinical characteristics, including nonstatistically different predrug QTc interval durations. Second, our study did not examine electrolyte imbalances, which could affect cardiac repolarization. However, it is unlikely that such changes would occur in the 2 or 3 min after antiemetic administration and last only a few minutes. Third, the study did not assess the effects of prophylaxis, only those of treatment.

To assess the risk of drug-induced arrhythmia, in addition to *in vitro* and *in vivo* studies, reports of adverse events are of great clinical significance. For both droperidol and ondansetron, cardiac arrhythmias have been reported. However, there is no published report of arrhythmia after low-dose droperidol in the treatment of PONV. The only available data have been reviewed by Habib and Gan[15] and extracted from the Food and Drug Administration safety database. For the 10 reported cases, a causal relation of droperidol administration seemed uncertain and has been a matter for extensive debate.[11–13] It is of interest to note that the only reported case of arrhythmia immediately after droperidol bolus occurred in one patient who received two other 5-HT_3 antagonists. Among them, dolasetron was given almost simultaneously with droperidol. Atrial fibrillation[16] and two cases of dysrhythmias[17] after administration of 4 mg ondansetron have also been reported.

The magnitude of average QTc interval lengthening observed in our study is considered to be associated with a probable potential for risk of torsade de pointes.[28] Furthermore, 12% of our patients reached absolute QTc interval values greater than 500 ms after droperidol (n = 4) or ondansetron (n = 6) administration. This criterion is considered a good predictor for increased risk of drug-induced torsade de pointes.[1,28] However, QT interval prolongation is only a surrogate marker for the risk of torsades de pointes, and the actual risk must be further evaluated for both drugs. Furthermore, standard criteria to interpret QT interval prolongation in clinical studies have been developed in patients who are different in many aspects from our postoperative vomiting patients.

Clinical Implications

Because of an increased risk of drug-induced arrhythmia, it is usually recommended to avoid QT interval–prolonging drugs in patients who have long QT intervals before drug administration.[29] With respect to these recommendations, in our postoperative vomiting patients, as many as 20% of them should not receive drugs that are suspected to prolong the QT interval, such as droperidol or 5-HT_3 antagonists.

When drugs that can prolong the QT interval are used, physicians should ensure that the potential benefits outweigh the risks. There are great benefits to treating PONV,[5] and from an "epidemiologic" point of view, antiemetic drugs seem to be safe. The occurrence of torsade de pointes is exceptional in the postanesthesia room. Moreover, the level of risk seems to be of comparable amplitude among droperidol and 5-HT_3 antagonists. In fact, although our study was not designed to compare both drugs, QTc interval prolongation does not seem to be different between low-dose droperidol and ondansetron. The rationale for measuring the QT interval before administration of droperidol and possibly 5-HT_3 antagonists also must be better supported by further studies.

The Food and Drug Administration recommended that electrocardiographic monitoring be performed for at least 2–3 h after droperidol administration.§§ In the eight patients in whom QTc measurements were obtained up to 3 h after droperidol, we observed a decrease in QTc interval duration over time.

§§ Food and Drug Administration: Information and warnings about droperidol. Available at: http://www.fda.gov/medwatch/SAFETY/2001/inapsine.htm. Accessed December 10, 2004.

Controversy about the use of low-dose droperidol has led to two approaches of the risk–benefit analysis. On one hand, if one considers that, based on its effect on QT interval duration, droperidol significantly increases the risk of torsades de pointes,[11,12] it can be expected that 5-HT_3 antagonists will be associated with a risk of similar amplitude because they also may produce QT interval prolongation. Then, the precautions issued by the Food and Drug Administration about droperidol use, *i.e.*, obtaining a 12-lead electrocardiogram before drug administration followed by several hours of electrocardiographic monitoring, should be extended to 5-HT_3 antagonists. If this were the case, approximately 20% of patients should be excluded from treatment for PONV by the two drugs we studied. On the other hand, if one considers that droperidol is associated with a very low risk,[9,10,27] except under certain circumstances that could increase the risk of arrhythmia (bradycardia, hypothermia, or hypokalemia), this cost-effective drug could be used routinely. Particular caution should be taken in women who are at increased risk of both PONV and drug-induced torsades de pointes.[30]

In conclusion, the risk of proarrhythmias seems to be very low after both droperidol and ondansetron. However, caution should be taken when these drugs are administered to treat PONV, in particular in the common situation of acquired postoperative long QT interval. Use of 5-HT_3 antagonists may not be superior to low-dose droperidol for the safe administration of antinausea vomiting agents in the postoperative room.

The authors thank all the nurses and auxiliary staff of the recovery room from the Department of Anesthesiology and Intensive Care of Beaujon University Hospital (Clichy, France) for their participation in the study. Sabine Holtzer, M.D., Brigitte Corda, M.D., Frédérique Le Corre, M.D. (Staff Anesthesiologists), and Philippe Juvin, M.D., Ph.D. (Professor of Anesthesiology), provided fruitful discussions at the times of study preparation; Fabrice Cook, M.D., and Sébastien Perbet, M.D. (Residents in Anesthesiology), contributed to the data collection; and Marie-Pierre Vinh (Chief Anesthetist Nurse) provided for technical support (all affiliated with the Department of Anesthesiology and Intensive Care, Beaujon Hospital, Clichy, France).

References

1. Roden DM: Drug-induced prolongation of the QT interval. N Engl J Med 2004; 350:1013–22

2. Michaloudis DG, Kanakoudis FS, Petrou AM, Konstantinidou AS, Pollard BJ: The effects of midazolam or propofol followed by suxamethonium on the QT interval in humans. Eur J Anaesthesiol 1996; 13:364–8

3. Kuenszberg E, Loeckinger A, Kleinsasser A, Lindner KH, Puehringer F, Hoermann C: Sevoflurane progressively prolongs the QT interval in unpremedicated female adults. Eur J Anaesthesiol 2000; 17:662–4

4. Schmeling WT, Warltier DC, McDonald DJ, Madsen KE, Atlee JL, Kampine JP: Prolongation of the QT interval by enflurane, isoflurane, and halothane in humans. Anesth Analg 1991; 72:137–44

5. Gan TJ, Meyer T, Apfel CC, Chung F, Davis PJ, Eubanks S, Kovac A, Philip BK, Sessler DI, Temo J, Tramer MR, Watcha M: Consensus guidelines for managing postoperative nausea and vomiting. Anesth Analg 2003; 97:62–71

6. Boike SC, Ilson B, Zariffa N, Jorkasky DK: Cardiovascular effects of i.v. granisetron at two administration rates and of ondansetron in healthy adults. Am J Health Syst Pharm 1997; 54:1172–6

7. Benedict CR, Arbogast R, Martin L, Patton L, Morrill B, Hahne W: Single-blind study of the effects of intravenous dolasetron mesylate versus ondansetron on electrocardiographic parameters in normal volunteers. J Cardiovasc Pharmacol 1996; 28:53–9

8. Lischke V, Behne M, Doelken P, Schledt U, Probst S, Vettermann J: Droperidol causes a dose-dependent prolongation of the QT interval. Anesth Analg 1994; 79:983–6

9. Bailey P, Norton R, Karan S: The FDA droperidol warning: Is it justified? ANESTHESIOLOGY 2002; 97:288–9

10. Gan TJ, White PF, Scuderi PE, Watcha MF, Kovac A: FDA "black box" warning regarding use of droperidol for postoperative nausea and vomiting: Is it justified? (letter). ANESTHESIOLOGY 2002; 97:287

11. Shafer SL: Safety of patients reason for FDA black box warning on droperidol. Anesth Analg 2004; 98:551–2

12. Chang N, Simone A, Schultheis L, Rappaport B: Reviewing case reports and the droperidol warning: FDA response (letter). Anesth Analg 2003; 97:1542

13. Dershwitz M: There should be a threshold dose for the FDA black-box warning on droperidol. Anesth Analg 2003; 97:1542–3

14. Drolet B, Zhang S, Deschenes D, Rail J, Nadeau S, Zhou Z, January CT, Turgeon J: Droperidol lengthens cardiac repolarization due to block of the rapid component of the delayed rectifier potassium current. J Cardiovasc Electrophysiol 1999; 10:1597–604

15. Habib AS, Gan TJ: Food and drug administration black box warning on the perioperative use of droperidol: a review of the cases. Anesth Analg 2003; 96:1377–9

16. Kasinath NS, Malak O, Tetzlaff J: Atrial fibrillation after ondansetron for the prevention and treatment of postoperative nausea and vomiting: A case report. Can J Anaesth 2003; 50:229–31

17. Baguley WA, Hay WT, Mackie KP, Cheney FW, Cullen BF: Cardiac dysrhythmias associated with the intravenous administration of ondansetron and metoclopramide. Anesth Analg 1997; 84:1380–1

18. Charbit B, Becquemont L, Lepere B, Peytavin G, Funck-Brentano C: Pharmacokinetic and pharmacodynamic interaction between grapefruit juice and halofantrine. Clin Pharmacol Ther 2002; 72:514–23

19. Gill JS, Zezulka AV, Beevers DG, Davies P: Relation between initial blood pressure and its fall with treatment. Lancet 1985; 1:567–9

20. Booker PD, Whyte SD, Ladusans EJ: Long QT syndrome and anaesthesia. Br J Anaesth 2003; 90:349–66

21. Mattu A, Brady WJ, Perron AD: Electrocardiographic manifestations of hypothermia. Am J Emerg Med 2002; 20:314–26

22. Heath BM, Terrar DA: Separation of the components of the delayed rectifier potassium current using selective blockers of IKr and IKs in guinea-pig isolated ventricular myocytes. Exp Physiol 1996; 81:587–603

23. Martynyuk AE, Morey TE, Raatikainen MJ, Seubert CN, Dennis DM: Ionic mechanisms mediating the differential effects of methohexital and thiopental on action potential duration in guinea pig and rabbit isolated ventricular myocytes. ANESTHESIOLOGY 1999; 90:156–64

24. Chen X, Yamakage M, Yamada Y, Tohse N, Namiki A: Inhibitory effects of volatile anesthetics on currents produced on heterologous expression of KvLQT1 and minK in Xenopus oocytes. Vascul Pharmacol 2002; 39:33–8

25. Katchman A, McGroary K, Kilborn M, Kornick C, Manfredi P, Woosley R, Ebert S: Influence of opioid agonists on cardiac human ether-a-go-go-related gene K(+) currents. J Pharmacol Exp Ther 2002; 303:688–94

26. Kuryshev YA, Brown AM, Wang L, Benedict CR, Rampe D: Interactions of the 5-hydroxytryptamine 3 antagonist class of antiemetic drugs with human cardiac ion channels. J Pharmacol Exp Ther 2000; 295:614–20

27. Zhang Y, Luo Z, White P: A model for evaluating droperidol's effect on the median QTc interval. Anesth Analg 2004; 98:1130–5

28. Shah RR: The significance of QT interval in drug development. Br J Clin Pharmacol 2002; 54:188–202

29. Al-Khatib SM, LaPointe NM, Kramer JM, Califf RM: What clinicians should know about the QT interval. JAMA 2003; 289:2120–7

30. Wolbrette D, Naccarelli G, Curtis A, Lehmann M, Kadish A: Gender differences in arrhythmias. Clin Cardiol 2002; 25:49–56