Anesthesiology 2005; 102:1101–5

Effect of Low-dose Droperidol on the QT Interval during and after General Anesthesia

A Placebo-controlled Study

Paul F. White, Ph.D., M.D., Dajun Song, M.D., Ph.D.,† Joao Abrao, M.D., Ph.D.,‡ Kevin W. Klein, M.D.,§ Bryan Navarette, M.S.‖*

Background: **Since the effects of antiemetic doses of droperidol on the QT interval have not been previously studied, the authors designed a randomized, double-blind, placebo-controlled study to evaluate the intraoperative and postoperative effects of small-dose droperidol (0.625 and 1.25 mg intravenous) on the QT interval when used for antiemetic prophylaxis during general anesthesia.**

Methods: **One hundred twenty outpatients undergoing otolaryngologic procedures with a standardized general anesthetic technique were enrolled in this study. After anesthetic induction and before the surgical incision, 60 patients were given either saline or 0.625 or 1.25 mg intravenous droperidol in a total volume of 2 ml. A standard electrocardiographic lead II was recorded immediately before and every minute after the injection of the study medication during a 10-min observation period. The QTc (QT interval corrected for heart rate) was evaluated from the recorded electrocardiographic strips. In 60 additional patients, a 12-lead electrocardiogram was obtained before and at specific intervals up to 2 h after surgery to assess the effects of droperidol and general anesthesia on the QTc. Any abnormal heartbeats or arrhythmias during the operation or the subsequent 2-h monitoring interval were also noted.**

Results: **Intravenous droperidol, 0.625 and 1.25 mg, prolonged the QT interval by an average of 15 ± 40 and 22 ± 41 ms, respectively, at 3–6 min after administration during general anesthesia, but these changes did not differ significantly from that seen with saline (12 ± 35 ms) (all values mean ± SD). There were no statistically significant differences among the three study groups in the number of patients with greater than 10% prolongation in QTc (*vs.* baseline). Although general anesthesia was associated with a 14- to 16-ms prolongation of the QTc interval in the early postoperative period, there was no evidence of droperidol-induced QTc prolongation after surgery. Finally, there were no ectopic heartbeats observed on any of the electrocardiographic rhythm strips or 12-lead recordings during the perioperative period.**

Conclusion: **Use of a small dose of droperidol (0.625–1.25 mg intravenous) for antiemetic prophylaxis during general anesthesia was not associated with a statistically significant increase in the QTc interval compared with saline. More importantly, there was no evidence of any droperidol-induced QTc prolongation immediately after surgery.**

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.

IT is widely accepted that small intravenous doses of droperidol (0.625–1.25 mg) are the most cost-effective single drug therapy for prevention of postoperative nausea and vomiting (PONV).[1–4] However, the US Food and Drug Administration (FDA) mandated a "black box" warning on droperidol requiring additional electrocardiographic monitoring because of an alleged increased risk of serious cardiac arrhythmias due to QT prolongation.[5,6] An unpublished FDA-sponsored study# suggested that the QTc prolongation effect peaks within 5 min after intravenous administration of droperidol. Despite the lack of creditable scientific evidence to support the recommendation for additional electrocardiographic monitoring before and after administering droperidol,[7–11] the FDA-imposed black box warning has lead to a marked reduction in the clinical use of droperidol for both prophylaxis and treatment of PONV.[12,13]

Drug-induced prolongation of the QT interval has been reported to increase the risk of severe adverse cardiovascular events (*e.g.*, torsades de pointes).[14] An earlier study by Lischke *et al.*[15] suggested that the effects of droperidol in prolonging the QT interval were dose related. Based on a recent mathematical reanalysis of these data,[16] we hypothesized that the small doses of droperidol (0.625–1.25 mg) used for antiemetic prophylaxis could be associated with a 10–20% prolongation in the median QTc interval. However, the magnitude and time course of the effect of antiemetic doses of droperidol on the QTc interval has not been previously studied.

Therefore, this randomized, double-blind, placebo-controlled study was designed to determine the effect of standard antiemetic doses of droperidol on the QT interval when administered during general anesthesia. The secondary objectives were to assess the effects of low-dose droperidol on PONV and adverse clinical cardiovascular outcomes.

* Professor and Holder of the Margaret Milam McDermott Distinguished Chair, † Clinical Research Fellow, ‡ Visiting Professor from Faculdade de Medicina do Triangulo Mineiro, Brazil, § Clinical Professor, ‖ Medical Student.

Received from the Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas. Submitted for publication July 20, 2004. Accepted for publication December 22, 2004. Supported in part by the Margaret Milam McDermott Distinguished Chair in Anesthesiology and the White Mountain Institute, a private not-for-profit foundation in Los Altos, California (Dr. Paul F. White, President).

Address reprint requests to Dr. White: Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, CS 2. 282, Dallas, Texas 75390-9068. Address electronic mail to: paul.white@utsouthwestern.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

Desai M, Pinto A, Adigun A, Hilligoss J, Haidar SH, Chang N, Rappaport B, Huang SM, Gorski JC, Hall SD: Pharmacokinetics and QT interval pharmacodynamics of single intravenous doses of droperidol. FDA Science Forum, 2003.

Materials and Methods

After obtaining approval by the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas, 120 outpatients with American Society of Anesthesiologists physical status I–III who were scheduled to undergo otolaryngologic surgical procedures provided informed consent and were enrolled in this two-part clinical study. Patients with clinically significant cardiac disease, atrioventricular conduction delays or bundle branch blocks, a history of alcohol or drug abuse within the past 3 months, or morbid obesity (body mass index > 40 kg/m^2) were excluded from participation in this study. Patients who had taken any antiemetic medication within 24 h before surgery or were pregnant or experiencing menstrual symptoms were also excluded. A detailed medical history and demographic information, including age, height, weight, and American Society of Anesthesiologists physical status, and history of previous PONV, motion sickness, or smoking were obtained from each patient.

A 12-lead electrocardiogram was obtained in the preoperative holding area before any preoperative medications were administered. At the time of arrival in the operating room, an automatic blood pressure cuff, five-lead electrocardiograph, capnograph, and pulse oximeter were applied. Mean arterial pressure, heart rate, end-tidal carbon dioxide, and oxygen saturation were measured at 1- to 5-min intervals throughout the intraoperative study period. General anesthesia was induced with 1.5–2 mg/kg propofol and 0.5–1 μg/kg intravenous remifentanil, and 0.6 mg/kg intravenous rocuronium was used to facilitate tracheal intubation. After intubation, anesthesia was maintained with 4% inspired desflurane (in an air–oxygen mixture) and a remifentanil infusion at 0.125 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Approximately 15 min before the surgical incision, 60 patients received one of three study medications based on a computer-generated random number table. The study medication consisted of either saline (control) or 0.625 or 1.25 mg droperidol, prepared in identical-appearing 2-ml syringes by an individual not involved in the study. The patients were maintained under stable anesthetic conditions without surgical stimulation for a minimum 10-min interval after injection of the study medication.

The standard electrocardiographic lead II was continuously recorded at a paper speed of 50 mm/s and an amplification of 0.1 mV/mm for 2–3 min before and every minute for a minimum of 10 min after the injection of the study medication. In both the operating and recovery rooms, the cardiac rhythm was continuously monitored using a standard lead II. The electrocardiographic measurements were independently performed by two investigators who were unaware of which of the three treatment groups the patient had been assigned to. Heart rate was calculated from the three R-R intervals preceding the measured QT intervals. The QT intervals were measured manually from the onset of the QRS complexes to the end of the T wave (defined as the intersection of the isoelectric line and the tangent of the maximal downward limb of the T wave). Each registered measurement was a mean of two consecutive QT intervals. The QT interval was adjusted for the patient's heart rate using the formula of Bazett[17] ($QTc = QT/R\text{-}R^{0.5}$). If the T-wave amplitude was too low (< 0.1 mV), the lead was excluded from the analysis.

In a follow-up study, 60 patients who had received either droperidol (1.25 mg intravenous) or saline (2 ml) after induction of anesthesia underwent repeated 12-lead electrocardiographic evaluations after arrival in the recovery room and at subsequent 1- and 2-h intervals. The QTc interval was automatically calculated by the Marquette® MAC® VU device (Milwaukee, WI) using the formula of Bazett. Finally, the incidences of nausea and vomiting/retching (requiring a "rescue" antiemetic drug), restlessness, dizziness, and headache were assessed at 4- and 24-h intervals after surgery in the initial study population.

Statistical Analyses

Results are presented as mean ($\pm$ SD), percentage, and number. A power analysis ($\alpha = 0.05$, $\beta = 80\%$) was performed before the initiation of the study using the software nQuery Advisor® version 1.0 (Statistical Solutions, Saugus, MA). This analysis suggested that 20 patients in each group should be adequate to detect a 15% or greater prolongation of the QTc interval in the droperidol groups *versus* the saline group assuming a mean QTc of 400 ms with an SD of 40 ms in the control group.[16] These electrocardiographic data were analyzed using analysis of variance, with a Bonferroni correction applied for multiple comparisons. The changes in the QTc intervals recorded on the serial electrocardiographic tracings were analyzed using repeated-measures analysis of variance. All QTc data were subjected to normality testing using the D'Agostino skewness, kurtosis, and omnibus tests after performing a log transformation of these data. The incidences of postoperative side effects were analyzed using chi-square test with Fisher exact test where appropriate. A P value of less than 0.05 was considered statistically significant.

Results

The three study groups were similar with respect to their demographic characteristics, durations of anesthesia, and total dosages of anesthetic and analgesic drugs, as well as intravenous fluid administration during the operation (table 1). The recovery times from the end of anesthesia to awakening (*i.e.*, eye opening on verbal command), orientation (*i.e.*, correctly stating name, date

Table 1. Demographic Data and Intraoperative Anesthetic Drug Dosages and Fluid Volumes in the Three Treatment Groups in the Initial Study

	Control	0.625 mg Droperidol	1.25 mg Droperidol
n	20	20	20
Age, yr	47 ± 14	45 ± 16	45 ± 15
Weight, kg	82 ± 22	81 ± 16	77 ± 21
Height, cm	168 ± 12	172 ± 12	169 ± 13
Sex, n, M/F	7/13	11/9	10/10
ASA physical status, n, I/II/III	6/13/1	6/12/2	6/14/0
Type of ENT procedure, n			
Tympanoplasty	4	4	5
Sinusotomy	3	4	2
Septoplasty	7	6	8
Other	6	6	5
Duration of anesthesia, min	156 ± 64	123 ± 56	164 ± 34
Total propofol, mg	155 ± 32	163 ± 60	153 ± 51
Total remifentanil, μg	1,318 ± 638	1,217 ± 733	1,127 ± 429
Total intravenous fluid, ml	1,356 ± 468	1,113 ± 484	1,622 ± 1,008

No significant differences among the three groups.

ASA = American Society of Anesthesiologists; ENT = ear, nose, and throat.

Table 2. Effects of the Study Medication on the Electrocardiographic QT Interval during the 10-min Observation Interval before the Start of Surgery in the Initial Three Treatment Groups

	Control	0.625 mg Droperidol	1.25 mg Droperidol
QT interval before injection, ms	406 ± 28	400 ± 56	396 ± 46
QTc before injection, ms	439 ± 28	435 ± 27	426 ± 47
QTc at 10 min after injection, ms	446 ± 35	449 ± 40	444 ± 52
QTc ≤ baseline at 10 min, n (%)	10 (50)	6 (30)	8 (40)
QTc prolongation 0–10% at 10 min, n (%)	8 (40)	11 (55)	10 (50)
QTc prolongation 10–25% at 10 min, n (%)	2 (10)	3 (15)	2 (10)
Mean maximum ΔQTc, ms*	12 ± 35	15 ± 40	22 ± 41
Maximum QTc prolongation, ms	58	120	133
Electrocardiographic rhythm disturbances, n	0	0	0

Data are presented as mean ± SD and n (%). No significant differences among the three groups.

* Maximum prolongation was observed at 3–6 min.

of birth, and location), and recovery room discharge were similar among the three groups. Although the 0.625- and 1.25-mg droperidol groups had lower overall incidences of nausea and vomiting compared with the saline group (15% and 20% *vs.* 45%, respectively), this difference only achieved statistical significance when the two droperidol groups were combined (*vs.* saline), because of the small group sizes.

The mean maximum QTc prolongation values in the 0.625- and 1.25-mg droperidol groups were 15 ± 40 and 22 ± 41 ms, respectively, at 3–6 min after administration of the study medication compared with 12 ± 35 ms in the saline group. The average QTc intervals were nonsignificantly prolonged in all three groups at 10 min after intravenous injection of the study medication (table 2). There were no differences among the three study groups with respect to the incidence of QTc prolongation greater than 10% of the baseline value. However, two patients in each of the droperidol groups had QTc prolongation lasting more than 60 ms during the 10-min observation period. The maximum prolongation of the QTc interval was 133 ms in a patient receiving 1.25 mg intravenous droperidol. There were no significant differences among the three groups with respect to hemodynamic changes during the 10-min observation period (table 3). In addition, postoperative side effects were also not significantly different among the three treatment groups (table 3). No electrocardiographic rhythm disturbances were observed during the continuous electrocardiographic monitoring in the operating room or in the postanesthesia care unit before discharge.

In the follow-up study involving preoperative and postoperative 12-lead electrocardiographic monitoring, the mean QTc intervals and changes in QTc (from baseline values) were similar in patients who did or did not receive 1.25 mg intravenous droperidol (table 4). However, the QTc was significantly prolonged (14–16 s) in both groups at the time of arrival in the recovery room compared with the baseline values ($P < 0.01$). No arrhythmias were observed on the 12-lead electrocardiographic tracings at any of the testing intervals.

Discussion

Use of small doses of droperidol (0.625–1.25 mg intravenous) for antiemetic prophylaxis was not associated with clinically significant prolongation of the QT interval during or immediately after surgery. Although these small antiemetic doses of droperidol were able to produce significant (> 10%) prolongation of the QT interval in 10–15% of the study patients, this effect was short lasting, and there was no evidence of any adverse effect on cardiac rhythm. The residual effect of general anesthesia was also associated with a small but statistically significant prolongation in the QTc at the time of arrival in the recovery room, both in those who did and in those who did not receive intraoperative droperidol. Given the lack of any direct evidence that use of droperidol in the therapeutic dosage range (0.625–1.25 mg intravenous) was associated with any clinically significant effects on the electrocardiogram or adverse cardiovascular outcomes, these data support the position that the current FDA recommendations for additional perioperative electrocardiographic monitoring are unnecessary and, in fact, wasteful of valuable healthcare resources.

Table 3. Changes in Intraoperative Hemodynamic Variables (during the 10-min Postinjection Period), Electrocardiographic Rhythm Disturbances, and Postoperative Adverse Effects in the Three Treatment Groups

	Control	0.625 mg Droperidol	1.25 mg Droperidol
Intraoperative hemodynamic variables			
Baseline			
MAP, mmHg	86 ± 15	86 ± 16	79 ± 23
HR, beats/min	71 ± 9	69 ± 25	72 ± 14
Maximum			
ΔMAP, mmHg	9 ± 20	15 ± 30	14 ± 25
ΔHR, beats/min	2 ± 11	8 ± 21	1 ± 20
At 10 min			
MAP, mmHg	75 ± 15	70 ± 24	64 ± 17
HR, beats/min	67 ± 8	67 ± 22	68 ± 14
Changes in electrocardiographic rhythm, n	0	0	0
Postoperative recovery times, min			
Awakening	9 ± 4	10 ± 5	7 ± 3
Orientation	16 ± 5	14 ± 5	14 ± 4
PACU discharge	99 ± 49	77 ± 27	86 ± 43
Postoperative adverse effects, n (%)			
Nausea	8 (40)	3 (15)	4 (20)
Vomiting	1 (5)	0	0
Restlessness	1 (5)	3 (15)	3 (15)
Dizziness	0	1 (5)	3 (15)
Headache	2 (10)	3 (15)	5 (25)

Data are presented as mean ± SD and n (%). No significant differences among the groups.

HR = heart rate; MAP = mean arterial pressure; PACU = postanesthesia care unit.

Table 4. Effects of 1.25 mg Intravenous Droperidol on the QTc Interval before and after Surgery as Assessed Using a 12-Lead Electrocardiogram in the Follow-up Study

	Control	1.25 mg Droperidol
n	30	30
Age, yr	47 ± 12	46 ± 14
Height, cm	171 ± 8	171 ± 8
Weight, cm	81 ± 18	88 ± 24
Type of ENT surgery, n		
Tympanoplasty	5	9
Sinusotomy	8	5
Septoplasty	3	5
Other	14	11
Surgery time, min	98 ± 59	104 ± 82
Anesthesia time, min	122 ± 62	129 ± 106
Baseline QTc value, ms	410 ± 17	415 ± 24
Postoperative QTc value, ms		
At arrival in the PACU	426 ± 28*	429 ± 26*
At 1 h after arrival	423 ± 23	422 ± 22
At 2 h after arrival	414 ± 19	415 ± 11
Changes from baseline, Δms		
At arrival in PACU	16 ± 26	14 ± 26
At 1 h after arrival	11 ± 25	6 ± 28
At 2 h after arrival	5 ± 9	3 ± 8

Data are presented as mean ± SD.

* Significantly different from the preoperative baseline QTc value, $P < 0.05$.

ENT = ear, nose, and throat; PACU = postanesthesia care unit.

A previous study involving higher doses of droperidol (0.1–0.25 mg/kg) suggested that this butyrophenone could produce dose-related prolongation of the QT interval.[15] Interestingly, despite the use of these high-doses of droperidol as part of a neurolept anesthetic technique for more than 30 yr,[18] there has not been a single report of a serious cardiac arrhythmia during or after anesthesia in the peer-reviewed literature. In carefully examining the specific case reports that lead the FDA to place a black box warning on the use of droperidol, investigators have concluded that "there is no evidence of a cause-and-effect relationship,"[11] and in most of the cases, there was "a more plausible explanation for the etiology of the described event."[19]

Food and Drug Administration officials have argued that the Food, Drug and Cosmetics Act allows that "reasonable evidence of association between drug and serious adverse event is evidence enough to place a warning in a drug label."[5] Curiously, despite ample evidence that the popular 5-hydroxytryptamine type 3 antagonists dolasetron and ondansetron prolong the QTc interval in a dose-related fashion for up to 4 h,[20] these drugs have not been issued black box warnings. In defense of the FDA decision, Shafer[6] argued that the mere fact that there is a mechanistic basis for droperidol to prolong QT[21,22] "paints a convincing story of genuine risk from droperidol for a very small number of patients." Because similar interactions have been reported between the 5-hydroxytryptamine type 3 antagonists and human cardiac ion channels,[23] it is unclear why this same reasoning would not also be applied to this popular class of antiemetic drugs.

Using a mathematical model to estimate the average prolongation of the median QTc interval by small doses of droperidol, Zhang *et al.*[16] reported that 0.625–1.25 mg intravenous droperidol would be expected to prolong the median QTc interval by 9–18 ms beyond the saline "control" values. The current clinical findings confirm these previous predications. However, even in the two patients displaying more than 100 ms prolongation of the QTc interval, there was no evidence of any ectopic electrocardiographic activity or changes in their cardiac rhythm. Of note, the maximum effect of droperidol on the QTc interval during general anesthesia occurred at 3–6 min after the intravenous bolus injection. Therefore, the FDA recommendation for prolonged electrocardiographic monitoring after administration of droperidol seems illogical.

This two-part study can be criticized because the group sizes were too small to detect rare cardiovascular events. However, we were able to demonstrate that even small, antiemetic doses of droperidol produce the predicted effect on the QTc interval.[16] Another potential criticism of this study relates to the method used to evaluate droperidol-induced QT prolongation. A recent

analysis by Sadanaga *et al.*[24] found that the overall accuracy of predicting QT prolongation was significantly increased (98.1%) when using the formula of Bazett compared with using any fixed QTc cutoff value. In fact, the formula of Bazett compared favorably to the formula of Friderica (98.7%) in improving the accuracy of evaluating QT prolongation.[24] Other investigators have similarly concluded that the formula of Bazett is at least as good as other proposed heart rate corrections for the QT interval.[25,26] Finally, these findings examined the effect of low-dose droperidol on the QTc interval of anesthetized patients and may not apply to situations where the drug is used for the *treatment* of PONV.

In light of these findings, we urge the FDA and the drug manufacturer (Akorn, Inc., Buffalo Grove, IL) to modify the black box warning to reflect a more reasonable position with respect to the clinical use of low-dose droperidol (< 2.5 mg intravenous) for the treatment and prevention of PONV. As stated in the consensus guidelines for managing PONV sponsored by the manufacturer of a competing 5-hydroxytryptamine type 3 antagonist,[27] droperidol would have been the panel's "overwhelming first choice for the prevention of PONV" were it not for the black box warning. From a societal cost–benefit perspective,[28,29] low-dose droperidol should be made available to practitioners for routine clinical use without the medical legal concerns engendered by the current black box warning in the droperidol package insert. As pointed out by Roden[30] in his recent review article on drug-induced prolongation of the QT interval, rare poorly understood side effects occur with many highly effective drugs, and "restrictions in the use of these drugs may harm more patients than it would help."

We conclude that 0.625–1.25 mg intravenous droperidol produces clinically insignificant prolongation of the QT interval and that the peak effect occurs less than 6 min after the intravenous bolus injection. Therefore, the current FDA recommendations for additional preoperative and postoperative electrocardiographic monitoring after administration of low-dose droperidol are unwarranted.

References

1. Tang J, Watcha MF, White PF: A comparison of costs and efficacy of ondansetron and droperidol as prophylactic antiemetic therapy for elective outpatient gynecologic procedures. Anesth Analg 1996; 83:304–13
2. Fortney JT, Gan TJ, Graczyk S, Wetchler B, Melson T, Khalil S, McKenzie R, Parrillo S, Glass PSA, Moote C, Wermeling D, Parasuraman TV, Duncan B, Creed MR: A comparison of the efficacy, safety, and patient satisfaction of ondansetron versus droperidol as antiemetics for elective outpatient surgical procedures. Anesth Analg 1998; 86:731–8
3. Hill RP, Lubarsky DA, Phillips-Bute B, Fortney JT, Creed MR, Glass PS, Gan TJ: Cost-effectiveness of prophylactic antiemetic therapy with ondansetron, droperidol, or placebo. ANESTHESIOLOGY 2000; 92:931–3
4. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I, Zernak C, Danner K, Jokela R, Pocock SJ, Trankler S, Kredel M, Biedler A, Sessler DI, Roewer N: A factorial trial of six interventions for prevention of postoperative nausea and vomiting. N Engl J Med 2004; 350:2441–51
5. Chang N, Simone A, Schultheis L, Rappaport B: Reviewing case reports and the droperidol warning: FDA response (letter). Anesth Analg 2003; 97:1542
6. Shafer SL: Safety of patients reason for FDA black box warning on droperidol (letter). Anesth Analg 2004; 98:551–2
7. 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
8. Young D: Black-box warning for droperidol surprises pharmacists. Am J Health Pharm 2002; 59:494, 497, 502–4
9. White PF: Droperidol: A cost-effective antiemetic for over thirty years. Anesth Analg 2002; 95:789–90
10. Dershwitz M: Droperidol: should the black box be light gray? J Clin Anesth 2002; 14:598–603
11. 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
12. Scuderi PE: Droperidol: Many questions, few answers. ANESTHESIOLOGY 2003; 98:289–90
13. Bailey P, White PF: Droperidol editorial: Making a mountain out of a mole hill! ANESTHESIOLOGY 2003; 99:760–1
14. Guy JM, Andre-Fouet X, Porte J, Bertrand M, Lamaud M, Verneyre H: Torsades de pointes and prolongation of the duration of QT interval after injection of droperidol. Ann Cardiol Angiol (Paris) 1991; 40:541–5
15. 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
16. Zhang Y, Luo Z, White PF: A model for evaluating droperidol's effect on the median QTc interval. Anesth Analg 2004; 98:1330–5
17. Bazett HC: An analysis of the time-relation of electrocardiograms. Heart 1920; 7:353–67
18. Zsigmond EK: Neurolept and dissociative anesthesia, Textbook of Intravenous Anesthesia. Edited by White PF. London, Williams & Wilkins, 1997, pp 393–403
19. Dershwitz M: There should be a threshold dose for the FDA black-box warning on droperidol. Anesth Analg 2003; 97:1542–3
20. 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
21. Priori SG, Barhanin J, Hauer RN, Haverkamp W, Jongsma HK, Kleber AG, McKenna WJ, Roden DM, Rudy Y, Schwartz K, Schwartz PJ, Towbin JA, Wilde AM: Genetic and molecular basis of cardiac arrhythmias: Impact on clinical management parts I and II. Circulation 1999; 99:518–28
22. Priori SG, Barhanin J, Hauer RN, Haverkamp W, Jongsma HK, Kleber AG, McKenna WJ, Roden DM, Rudy Y, Schwartz K, Schwartz PJ, Towbin JA, Wilde AM: Genetic and molecular basis of cardiac arrhythmias: Impact on clinical management part III. Circulation 1999; 99:674–81
23. 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
24. Sadanaga T, Sadanaga F, Yao H, Fujishima M: Hart rate dependent modification of the QTc cut-off values can improve accurate evaluation of QT prolongation. Am J Cardiol 2004; 93:772–5
25. Brouwer J, Van Den Berg MP, Grobbee DE, Haaksma J, Wilde AA: Diagnostic performance of various QTc interval formulas in a large family with long QT syndrome type 3: Bazett's formula not so bad after all . . . Ann Noninvasive Electrocardiol 2003; 8:269–74
26. Liu B, Juurlink DN: Drugs and the QT interval: Caveat doctor. N Engl J Med 2004; 351:1053–96
27. 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
28. Watcha MF: The cost-effective management of postoperative nausea and vomiting. ANESTHESIOLOGY 2000; 92:931–3
29. White PF: Prevention of postoperative nausea and vomiting: A multimodal solution to a persistent problem. N Engl J Med 2004; 350:2511–2
30. Roden DM: Drug-induced prolongation of the QT interval. N Engl J Med 2004; 350:1013–22