

Bon Secours Richmond
Pharmacy & Therapeutics Committees
Droperidol
7/05

Recommendations:

- Use of droperidol for prophylaxis and treatment of PONV will be unrestricted in doses commonly used, 1.25 mg or less in adults with a maximum total daily dose of 5 mg.
- Droperidol 0.625 mg is recommended for prophylaxis and treatment of PONV and opioid induced nausea and vomiting and will be placed on physician preprinted order forms.
- Mandatory ECG screening for all patients is not recommended.

Findings:

- A warning was added to the package insert in 12/2001, which was based on two studies, a British study in psychiatric patients and a German dose ranging study using doses of 0.1 mg/kg, 0.175 mg/kg, and 0.25 mg/kg which caused a 37 ms, 44 ms, and 59 ms increase in QTc interval, respectively versus controls, and adverse drug reactions reported to MedWatch. Eighty three percent of the MedWatch reports were received from nations outside of the United States and 49% of these describe fatalities from doses of 50 mg or more.
- A second study of the electrocardiographic variations caused by the drug. Fifty five unselected patients under the same conditions (general anesthesia) were given droperidol (0.25 mg/kg IV, 17.5 mg for 70 kg patient). Significant prolongation of the QT interval was seen in 70% of cases by the end of the first minute. QT interval and the ratio of QTm (measured) over QTt increased from 387 +/- 34 ms to 423 +/- 37 ms (p less than 0.0001) and from 1.06 +/- 0.08 to 1.28 +/- 0.1 (p less than 0.001) respectively. These changes could favor the onset of TDP.
- Low doses of droperidol 0.625 mg-1.25 mg during general anesthesia have been shown to cause increase in QT interval by 15 and 22 ms respectively. *Anesthesiology*. 2005 Jun;102(6):1101-1105.
- A recent study demonstrated that both droperidol 0.75 mg and ondansetron 4 mg IV has similar increases in QTc interval, 17 and 20 ms respectively. *Anesthesiology* 2005 Jun;102(6):1094-110
- A prior warning in the package insert about cases of sudden death at high doses (greater than 25 mg) in patients at risk for cardiac dysrhythmias.
- The drug had been on the market for 31 years.
- Twenty-five million doses were sold world wide in 2000. Eleven million doses, 2.5 mg, were sold in the USA in 2001.
- The FDA approved adult dose is 2.5 mg once, followed by 1.25 mg as needed, as of 1/2002. Prior to this time doses of 2.5-10 mg were recommended in adults. Droperidol is currently indicated for prophylaxis of PONV.
- Droperidol, 0.625-1.25 mg, is widely accepted as a first line therapy for prophylaxis and treatment of PONV. NNT for prevention of PONV is 5-6 for both ondansetron and droperidol and side effect profiles are similar.
- Droperidol dose in psychosis used in Europe is 5-20 mg orally q4-8 h prn, up to 10 mg IM, or 5-15 mg IV q4-6 hr prn.
- Several authors requested information from the FDA under the Freedom of Information Act to clarify the changes to the package insert.
 - Bailey P. *Anesthesiology* 2002;97: 288-89
 - 273 cases reported (USA and other countries) from 11/1/1997 to 1/2/2002
 - 127 had serious outcome (death, prolonged hospitalization, or were life threatening)
 - 74% (94/127) were from foreign sources
 - 89 deaths were reported
 - Droperidol dose

- 2 deaths with doses less than or equal to 2.5 mg
 - Most deaths involved droperidol doses that ranged from 25-250 mg
 - Dose not documented in 14 deaths
 - Cardiac morbidity possibly played a role in 74 of 127 serious outcomes
 - 57/74 were associated with large doses
 - 17/74 were with doses 2.5 mg or less
 - 10/74 were with doses of 1.25 mg or less (FDA approved dose)
 - Multiple drugs were administered, including other antiemetic and antipsychotics
 - 3/17 droperidol was the only drug administered at 2.5 mg or less
 - 5 patients experienced either ventricular tachycardia (2) or torsades (3), but not prolonged QT. One case was fatal
 - Dershwitz M. Journal of Clinical Anesthesia 2002;14:598-603 requested the actual clinical information submitted to the FDA for the 19 reported events describing cardiac or respiratory effects with doses less than 10 mg. See attached article
 - Habib AS. Anesthesia Analgesia 2003;96:1377-9 request case reports for patients with cardiac adverse events with doses of droperidol 1.25 mg or less. See attached article
 - Mullins M. American Journal of Emergency Medicine 2004;22:27-28
- There is no consensus regarding the precise degree of QT prolongation that is clinically significant, although most would consider a QT interval of more than 500 ms or a change in QT interval of more than 60 ms to represent at least some risk.
- In vitro, droperidol induces potassium channel blockage.
- The maximum effect of injectible droperidol on QTc interval occurs 3-6 minutes post injection.
- During Torsades the heart produces essentially no effective cardiac output. If the episode lasts more than about 10 seconds unconsciousness results and possibly tonic-clonic seizure due to brain hypoxia.
- Females are at a greater risk for developing Torsades
- Symptoms of torsades
 - Lightheaded
 - Dizzy
 - Awareness of heart fluttering
 - Transient shortness of breath
 - A sensation of their breath catching for a moment
- Risk factors
 - Bradycardia, especially with occasional premature beats
 - Congenital long QT syndrome
 - Hypokalemia
 - Hypomagnesemia
 - Stimulant conditions such as exercise, emotion, or use of drugs like dopamine, epinephrine or even albuterol
 - Female between menarche and menopause
 - Congenital abnormalities of cardiac membrane channels and use of various drugs, which interact with membrane channels (HERG potassium channel) to lengthen QT.
- Drugs with a high risk of torsades: amiodarone, arsenic trioxide, bepridil, chloroquine, cisapride, clarithromycin, disopyramide, dofetilide, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, pentamidine, pimozone, procainamide, quinidine, sotalol, sparfloxacin, and thioridazine. www.torsades.org

Anesth Analg. 1994 Nov;79(5):983-6.

Droperidol causes a dose-dependent prolongation of the QT interval.

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To further investigate possible prolongation of the frequency-corrected QT interval (QTc interval) after administration of droperidol (DRO), we studied 40 surgical patients who were randomly assigned to one of three groups, receiving an intravenous (IV) injection of either 0.1 mg/kg (Group 1, n = 10), 0.175 mg/kg (Group 2, n = 10), or 0.25 mg/kg (Group 3, n = 20) of DRO at induction of anesthesia. The QTc interval, heart rate, and arterial pressure were registered before and 1, 2, 3, 4, 5, 7.5, and 10 min after the respective dose injection. Significant prolongations of the median QTc interval were found in patients from all groups, ranging from 37 ms (8.0%) in Group 1, to 44 ms (10.6%) in Group 2, to 59 ms (14.9%) in Group 3, when compared with control. The heart rate showed a significant increase in all groups. Mean arterial pressure (MAP) was slightly but significantly decreased in Groups 1 and 3. Prolongation of the QTc interval is a predictable and dose-dependent side effect after injection of high-dose DRO.

Lancet. 2000 Mar 25;355(9209):1048-52.

Comment in:

- [Lancet. 2000 Jul 1;356\(9223\):75-6.](#)
- [Lancet. 2000 Jul 29;356\(9227\):428.](#)
- [Lancet. 2000 May 20;355\(9217\):1824-5.](#)
- [Lancet. 2000 May 20;355\(9217\):1825.](#)

QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients.

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BACKGROUND: Sudden unexplained death in psychiatric patients may be due to drug-induced arrhythmia, of which lengthening of the rate-corrected QT interval (QTc) on the electrocardiogram is a predictive marker. We estimated the point prevalence of QTc lengthening in psychiatric patients and the effects of various psychotropic drugs. **METHODS:** Electrocardiograms were obtained from 101 healthy reference individuals and 495 psychiatric patients in various inpatient and community settings and were analysed with a previously validated digitiser technique. Patients with and without QTc lengthening, QTc dispersion, and T-wave abnormality were compared by logistic regression to calculate odds ratios for predictive variables. **FINDINGS:** Abnormal QTc was defined from the healthy reference group as more than 456 ms and was present in 8% (40 of 495) of patients. Age over 65 years (odds ratio 3.0 [95% CI 1.1-8.3]), use of tricyclic antidepressants (4.4 [1.6-12.1]), thioridazine (5.4 [2.0-13.7]), and droperidol (6.7 [1.8-24.8]) were robust predictors of QTc lengthening, as was antipsychotic dose (high dose 5.3 [1.2-24.4]; very high dose 8.2 [1.5-43.6]). Abnormal QT dispersion or T-wave abnormalities were not significantly associated with antipsychotic treatment, but were associated with lithium therapy. **INTERPRETATION:** Antipsychotic drugs cause QTc lengthening in a dose-related manner. Risks are substantially higher for thioridazine and droperidol. These drugs may therefore confer an increased risk of drug-induced arrhythmia.

Ann Cardiol Angeiol (Paris). 1991 Nov;40(9):541-5.

[Torsades de pointes and prolongation of the duration of QT interval after injection of droperidol]

[Article in French]

Guy JM, Andre-Fouet X, Porte J, Bertrand M, Lamaud M, Verneyre H.

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Following a case of torsades de pointe (TDP) after the injection of droperidol (D), the authors studied the electrocardiographic variations caused by the drug. Fifty five unselected patients under the same conditions (general anesthesia) were given D (0.25 mg/kg IV). Significant prolongation of the QT interval was seen in 70% of cases by the end of the first minute. QT interval and the ratio of QTm (measured) over QTt increased from 387 +/- 34 ms to 423 +/- 37 ms (p less than 0.0001) and from 1.06 +/- 0.08 to 1.28 +/- 0.1 (p less than 0.001) respectively. These changes could favourise the onset of TDP. Although exceptional in terms of the extensive use of the neuroleptic in question, this possibility indicates the need for monitoring of the duration of QT before and during treatment with droperidol and for prescription of the drug to be avoided in circumstances known to be propitious to this arrhythmia (bradycardia, hypokalemia, anti-arrhythmic drugs).

Ann Emerg Med. 2003 Apr;41(4):546-58. Comment in:

- [Ann Emerg Med. 2003 Apr;41\(4\):559-60.](#)
- [Ann Emerg Med. 2004 Jan;43\(1\):139-40.](#)

Droperidol, QT prolongation, and sudden death: what is the evidence?

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STUDY OBJECTIVE: Droperidol is a butyrophenone commonly used as an antiemetic and antipsychotic in the United States since US Food and Drug Administration (FDA) approval in 1970. Its labeling has recently been revised, with a black box warning for cases of QT prolongation leading to torsades de pointes and death. A black box warning is applied when serious adverse drug reactions are uncovered for medications. We sought to examine the evidence of a causal association suggested by the black box warning to aid clinicians in their risk-benefit analyses regarding further use of droperidol. **METHODS:** A literature search was undertaken to determine the evidence regarding the association between droperidol and QT prolongation or torsades de pointes. The evidence was then evaluated by using evidence-based medicine principles. In addition, a review of the FDA regulatory process is presented. **RESULTS:** Three clinical studies, 1 published abstract, and 7 case reports were reviewed. Available postmarketing surveillance data (MedWatch reports) were also reviewed. Applying the criteria of evidence-based medicine and Hill's criteria, the evidence is not convincing for a causal relationship between therapeutic droperidol administration and life-threatening cardiac events. **CONCLUSION:** The recent black box warning appears to have originated from postmarketing surveillance data rather than data reported in the peer-reviewed medical literature. Ongoing monitoring of drug safety and more definitive study appear appropriate.

Pharmacotherapy. 2003 Jul;23(7):881-908.

Clinical relevance and management of drug-related QT interval prolongation.

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Much attention recently has focused on drugs that prolong the QT interval, potentially leading to fatal cardiac dysrhythmias (e.g., torsade de pointes). We provide a detailed review of the published evidence that supports or does not support an association between drugs and their risk of QT prolongation. The mechanism of drug-induced QT prolongation is reviewed briefly, followed by an extensive evaluation of drugs associated with QT prolongation, torsade de pointes, or both. Drugs associated with QT prolongation are identified as having definite, probable, or proposed associations. The role of the clinician in the prevention and management of QT prolongation, drug-drug interactions that may occur with agents known to affect the QT interval, and the impact of this adverse effect on the regulatory process are addressed.

2: JAMA. 2003 Apr 23-30;289(16):2120-7.

Erratum in:

- JAMA. 2003 Sep 10;290(10):1318.

Comment in:

- [JAMA. 2003 Aug 27;290\(8\):1025; author reply 1026.](#)
- [JAMA. 2003 Aug 27;290\(8\):1025; author reply 1026.](#)
- [JAMA. 2003 Aug 27;290\(8\):1026; author reply 1026.](#)

What clinicians should know about the QT interval.

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CONTEXT: Of the several factors implicated in causing QT interval prolongation and torsades de pointes, errors in the use of medications that may prolong this interval deserve special attention. **OBJECTIVE:** To systematically summarize the available clinical data on the QT interval and to offer improved recommendations for the use of QT-prolonging medications. **DATA SOURCES:** We searched MEDLINE from 1966 through 2002 for all English-language articles related to the QT interval. Additional data sources included bibliographies of articles identified on MEDLINE, a survey of experts, and data

presented at a meeting of experts on long QT syndrome. **STUDY SELECTION:** We selected for review registries and case series examining clinical outcomes of patients with prolonged QT interval and the effect of different methods of measurement of the QT interval on patient outcomes. Ten studies were identified, of which 6 were included in the analysis. **DATA EXTRACTION:** Data quality was determined by publication in the peer-reviewed literature. **DATA SYNTHESIS:** Optimal measurement of the QT interval is problematic because of lack of standardization and lack of data regarding the best way to adjust for heart rate. Reliable information on the proper use of QT-prolonging medications is scarce. Although a QT interval of at least 500 milliseconds generally has been shown to correlate with a higher risk of torsades de pointes, there is no established threshold below which prolongation of the QT interval is considered free of proarrhythmic risk. The risk of torsades de pointes should be assessed in patients who are about to begin taking a QT-prolonging medication. Although inadequate clinical studies preclude prediction of absolute risk for individual patients, particularly high-risk situations can be defined based on clinical variables. We propose recommendations on proper monitoring of the QT interval in patients receiving QT-prolonging medications. **CONCLUSION:** Although the use of QT-prolonging medications can predispose to torsades de pointes, there is a relative paucity of information that can help clinicians and patients make optimal informed decisions about how best to minimize the risk of this serious complication.

Drug Saf. 2002;25(4):263-86.

Safety of non-antiarrhythmic drugs that prolong the QT interval or induce torsade de pointes: an overview.

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The long and growing list of non-antiarrhythmic drugs associated with prolongation of the QT interval of the electrocardiogram has generated concern not only for regulatory interventions leading to drug withdrawal, but also for the unjustified view that QT prolongation is usually an intrinsic effect of a whole therapeutic class [e.g. histamine H(1) receptor antagonists (antihistamines)], whereas, in many cases, it is displayed only by some compounds within a given class of non-antiarrhythmic drugs because of an effect on cardiac repolarisation. We provide an overview of the different classes of non-antiarrhythmic drugs reported to prolong the QT interval (e.g. antihistamines, antipsychotics, antidepressants and macrolides) and discusses the clinical relevance of the QT prolonging effect. Drug-induced torsade de pointes are sometimes considered idiosyncratic, totally unpredictable adverse drug reactions, whereas a number of risk factors for their occurrence is now recognised. Widespread knowledge of these risk factors and implementation of a comprehensive list of QT prolonging drugs becomes an important issue. Risk factors include congenital long QT syndrome, clinically significant bradycardia or heart disease, electrolyte imbalance (especially hypokalaemia, hypomagnesaemia, hypocalcaemia), impaired hepatic/renal function, concomitant treatment with other drugs with known potential for pharmacokinetic/pharmacodynamic interactions (e.g. azole antifungals, macrolide antibacterials and class I or III antiarrhythmic agents). This review provides insight into the strategies that should be followed during a drug development program when a drug is suspected to affect the QT interval. The factors limiting the predictive value of preclinical and clinical studies are also outlined. The sensitivity of preclinical tests (i.e. their ability to label as positive those drugs with a real risk of inducing QT prolongation in humans) is sufficiently good, but their specificity (i.e. their ability to label as negative those drugs carrying no risk) is not well established. Verapamil is a notable example of a false positive: it blocks human ether-a-go-go-related (HERG) K(+) channels, but is reported to have little potential to trigger torsade de pointes. Although inhibition of HERG K(+) channels has been proposed as a primary test for screening purposes, it is important to remember that several ion currents are involved in the generation of the cardiac potential and that metabolites must be specifically tested in this *in vitro* test. At the present state of knowledge, no preclinical model has an absolute predictive value or can be considered as a gold standard. Therefore, the use of several models facilitates decision making and is recommended by most experts in the field.

Drug Saf. 2001;24(8):575-85.

Is gender a risk factor for adverse drug reactions? The example of drug-induced long QT syndrome.

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Drug-induced torsade de pointes is a rare life-threatening adverse drug reaction (ADR) which is strongly influenced by gender. Drugs that prolong cardiac repolarisation include antiarrhythmics, gastrokinetics, antipsychotics, antihistamines and antibacterials. Such drugs share the potential to block cardiac voltage-gated potassium channels, particularly the rapid component (I(Kr)) of the delayed rectifier potassium current (I(K)). By doing so, such drugs usually, but not always, prolong the QT interval. Even if the electrocardiographic signs are subdued, the underlying blockade of I(Kr) current may precipitate the occurrence of arrhythmia. Women are perceived to be more prone to ADRs than men. Such a propensity may result from gender-associated differences in drug exposure, in the number of drugs prescribed (polypharmacy), in drug pharmacology, as well as from possible differences in the way the adverse event is perceived. A prolonged QT interval on the electrocardiogram (time that elapses from the onset of the cardiac ventricular depolarisation to the completion of its repolarisation) is associated with the occurrence of torsade de pointes and related ventricular arrhythmias. The QT interval is

influenced by heart rate, autonomic nervous system, electrolyte disturbances and above all, drugs that block potassium channels. Two-thirds of the cases of drug-induced torsade de pointes occur in women. Therefore, this adverse effect represents a perfect example of gender differences impairing women's health. Clinical and experimental studies show that female gender is associated with a longer corrected QT interval at baseline and a greater response to drugs that block I(Kr), both of which facilitate the emergence of arrhythmia. This results most likely from a specific regulation of ionic channel expression (potassium, calcium, etc) by sex steroids, even though nongenomic effects may play a role as well. Estrogens facilitate bradycardia-induced prolongation of the QT interval and the emergence of arrhythmia whereas androgens shorten the QT interval and blunt the QT response to drugs. Hence, underlying genetic defects of potassium channels that may be asymptomatic in normal conditions, may precipitate drug-induced arrhythmia in women more frequently than in men. Even in the presence of a drug that mildly blocks I(Kr) and seldom prolongs the QT interval, women are still more prone to drug-induced torsade de pointes, due to their reduced cardiac 'repolarisation reserve'. This is an important aspect of I(Kr) blockade to be aware of during the development of new drugs.

5: Am J Cardiol. 1993 Aug 26;72(6):4B-9B.

Mechanisms and models to predict a QTc effect.

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Prolongation of the QT interval with consequent ventricular tachyarrhythmias may arise in the context of bradycardia (pause dependent) or may reflect sympathetic imbalances (adrenergic dependent). The normal repolarization process of ventricular myocardial cells is not entirely synchronous; some cells recover early and some later, resulting in a normal heterogeneity in refractoriness among ventricular cells during the inscription of the T wave. If the normal heterogeneity in ventricular repolarization is increased, as can occur following administration of some class IA and class III antiarrhythmic agents, then the QT interval will be prolonged. All-or-none action potentials can be evoked only in cells that have repolarized to a critical membrane potential of about -60 mV. Thus, the late-recovering cells (which terminate the T wave) may still be refractory and incapable of generating propagated action potentials while the early-recovering cells (which initiate the T wave) are fully excitable. In normal hearts, the period between repolarization of the earliest and the latest cells is insufficient to allow even very premature ventricular beats that occur early during the T wave (R-on-T phenomenon) to precipitate a sustained tachyarrhythmia. When the recovery process among ventricular cells becomes more inhomogeneous, however, as in the prolonged QT syndrome, the accompanying increased heterogeneity in ventricular repolarization and refractoriness can lead to the development of malignant ventricular arrhythmias, including torsades de pointes. Any drug that increases the dispersion of the repolarization process may prolong the QT interval and raise the potential for arrhythmias. (ABSTRACT TRUNCATED AT 250 WORDS)

Drugs. 2002;62(11):1649-71.

Antipsychotic-related QTc prolongation, torsade de pointes and sudden death.

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Sudden unexpected deaths have been reported with antipsychotic use since the early 1960s. In some cases the antipsychotic may be unrelated to death, but in others it appears to be a causal factor. Antipsychotics can cause sudden death by several mechanisms, but particular interest has centred on torsade de pointes (TdP), a polymorphic ventricular arrhythmia that can progress to ventricular fibrillation and sudden death. The QTc interval is a heart rate-corrected value that represents the time between the onset of electrical depolarisation of the ventricles and the end of repolarisation. Prolongation of the QTc interval is a surrogate marker for the ability of a drug to cause TdP. In individual patients an absolute QTc interval of >500 msec or an increase of 60 msec from baseline is regarded as indicating an increased risk of TdP. However, TdP can occur with lower QTc values or changes. Concern about a relationship between QTc prolongation, TdP and sudden death applies to a wide range of drugs and has led to the withdrawal or restricted labelling of several. Among antipsychotics available in the UK, sertindole was voluntarily suspended, droperidol was withdrawn, and restricted labelling introduced for thioridazine and pimozide. The degree of QTc prolongation is dose dependent and varies between antipsychotics reflecting their different capacity to block cardiac ion channels. Significant prolongation is not a class effect. Among currently available agents, thioridazine and ziprasidone are associated with the greatest QTc prolongation. Virtually all drugs known to cause TdP block the rapidly activating component of the delayed rectifier potassium current (I(kr)). Arrhythmias are more likely to occur if drug-induced QTc prolongation coexists with other risk factors, such as individual susceptibility, presence of congenital long QT syndromes, heart failure, bradycardia, electrolyte imbalance, overdose of a QTc prolonging drug, female sex, restraint, old age, hepatic or renal impairment, and slow metaboliser status. Pharmacodynamic and pharmacokinetic interactions can also increase the risk of arrhythmias. Further research is needed to quantify the risk of sudden death with antipsychotics. The

risk should be viewed in the context of the overall risks and benefits of antipsychotic treatment. It seems prudent, where possible, to select antipsychotics that are not associated with marked QTc prolongation. If use of a QTc-prolonging drug is warranted, then measures to reduce the risk should be adopted.

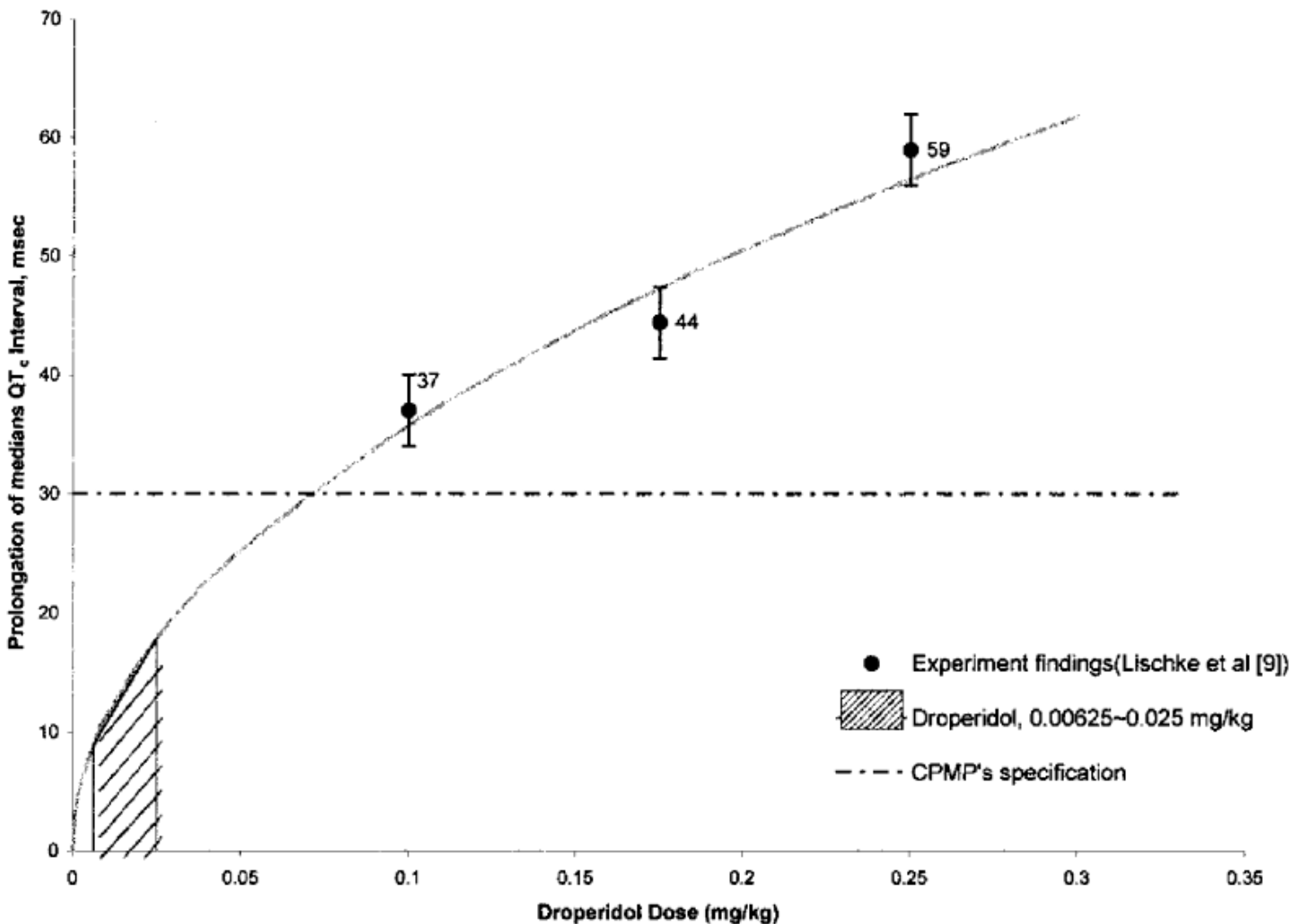
Anesth Analg. 2004 May;98(5):1330-5, table of contents.

A model for evaluating droperidol's effect on the median QTc interval.

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Controversy surrounds the use of the antiemetic droperidol, because of the Food and Drug Administration-imposed "black box" warning alleging that even small doses of the drug can lead to serious (even fatal) arrhythmias when it is used for antiemetic prophylaxis during the perioperative period. We used mathematical modeling of electrocardiographic QT interval data published in a peer-reviewed manuscript to evaluate the relationship between the dose of droperidol (0.1-0.25 mg/kg i.v.) and QT(c) prolongation. In comparing the calculated QT(c) values based on the logarithm model (27-63 ms), the linear model (27-67 ms) and the square-root model (36-57 ms) to the actual measured QT(c) values (37-59 ms), the square-root model provided the best simulation of the experimental findings. Other models that we evaluated included the polynomial model and various exponent models (e.g., quartic-root model, cubic-root model, square model, and cubic model). The estimated median prolongation of the median QT(c) interval produced by droperidol 0.625-1.25 mg i.v. would vary from 9 +/- 3 to 18 +/- 3 ms. Therefore, this regression analysis suggests that small "antiemetic" doses of droperidol (< or =1.25 mg) would be unlikely to produce proarrhythmogenic effects in the perioperative period. IMPLICATIONS: Using a square-root curve fit model to evaluate the relationship between the dose of droperidol and QT(c) prolongation, small-dose droperidol (0.625-1.25 mg i.v.) would be expected to produce <30-ms prolongation of the QT(c) interval. Therefore, small "antiemetic" doses of droperidol would not be expected to produce proarrhythmogenic effects when used for prophylaxis in surgical patients.



Anesthesiology. 2005 Jun;102(6):1101-1105.

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

Anesthesia: A Placebo-controlled Study.

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* Professor and Holder of the Margaret Milam McDermott Distinguished Chair, dagger Clinical Research Fellow, double dagger Visiting Professor from Faculdade de Medicina do Triangulo Mineiro, Brazil, section sign Clinical Professor, parallel Medical Student.

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.

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.

Anesthesiology. 2005 Jun;102(6):1094-1100.

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

Charbit B, Albaladejo P, Funck-Brentano C, Legrand M, Samain E, Marty J.

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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.

3: Paediatr Anaesth. 2004 Oct;14(10):831-7.

Comment in: [Paediatr Anaesth. 2004 Oct;14\(10\):807-9.](#)

Droperidol for perioperative sedation causes a transient prolongation of the QTc time in children under volatile anesthesia.

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BACKGROUND: Droperidol is useful for postoperative sedation in infants and children after cardiac surgery because it provides sedation and akinesia with minimal respiratory depression. However, droperidol has been associated with QT prolongation and ventricular arrhythmias. We investigated, if neuroleptanalgesic doses of droperidol led to QT prolongation and cardiac arrhythmias in children undergoing cardiac surgery. **METHODS:** We retrospectively analysed electrocardiogram rhythm strips that were obtained before and in time increments after a 100 microg x kg(-1) intravenous bolus of droperidol in 20 children undergoing cardiac surgery. The longest QT interval was determined in each ECG and corrected for heart rate (QTc). All arrhythmias were recorded. **RESULTS:** Droperidol led to a significant increase in QTc time that was still present at 15 min but had resolved within 30 min after the bolus. No associated arrhythmias were observed. **CONCLUSIONS:** The statistically significant prolongation of QTc time after a sedative dose of droperidol is of concern because it may increase the risk for malignant cardiac arrhythmias. A large, prospective study is necessary to identify the true risk for arrhythmias after droperidol in this patient population, but our study suggests that any arrhythmogenic risk, if present, will be very transient, since the increase in QTc time was limited to a period of less than 30 min after the bolus. Copyright 2004 Blackwell Publishing Ltd.

J Clin Pharmacol. 1998 Feb;38(2):160-5.

Droperidol elimination after cardiopulmonary bypass surgery.

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A high-dose (0.75 to 2.8 mg/kg) pharmacokinetic study of droperidol was undertaken in patients during the recovery phase

after cardiac surgery involving hypothermic cardiopulmonary bypass (CPB). The elimination half-life of droperidol in these patients, determined from concentration-time data obtained after CPB, was significantly prolonged relative to previously reported mean values in younger surgical patients not undergoing CPB and receiving lower doses of the drug (0.05-0.20 mg/kg). On stratification of the patients by droperidol dose, there was an inverse correlation between the size of the dose and the elimination half-life of droperidol: mean half-life decreased as mean dose increased. This difference in elimination half-life was not related to the duration of the CPB procedure, or the total anesthetic time, both of which were not significantly different between the patient groups receiving the three different doses of droperidol. The magnitude or duration of hypothermia after CPB did not differ between the three patient groups. The differences in half-lives are more likely due to the clinical condition of the patients, such that the patients who received the higher doses of droperidol were also judged clinically to be less ill and thus eliminated droperidol more efficiently. This hypothesis, however, could not be supported due to the small number of patients studied. The results obtained in this study indicate that droperidol elimination is significantly prolonged after high-dose administration to elderly patients undergoing hypothermic CPB procedures during cardiac surgery.

Br J Anaesth. 1988 Sep;61(3):297-301.

Pharmacokinetics of droperidol in surgical patients under different conditions of anaesthesia.

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The pharmacokinetics of droperidol were studied in 42 surgical patients using doses of 5, 10 and 15 mg i.v., in association with neuroleptanalgesia or volatile anaesthetics. Plasma concentrations of droperidol were measured by radioimmunoassay. During neuroleptanalgesia, droperidol kinetics were linear over the dose range tested: the overall mean elimination half-life was 127 min, V_{dss} 103 litre and the plasma clearance 732 ml min⁻¹. The kinetics of droperidol were similar under neuroleptanalgesia and under anaesthesia with halothane or enflurane. There was no significant correlation between the volume of distribution or clearance with age (14-65 yr) or body weight (48-90 kg).

Anesthesiology. 1986 Apr;64(4):486-9.

The pharmacokinetics of droperidol in anesthetized patients.

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A pharmacokinetic study of droperidol was performed in ten anesthetized patients receiving an intravenous bolus dose of 150 micrograms/kg of droperidol. Plasma concentrations were measured using a specific radioimmunoassay method. The pharmacokinetics of droperidol can be described according to a three-compartment open model. The mean (+/- SD) half-life for the rapid ($t_{1/2\text{ pi}}$) and slow distribution ($t_{1/2\text{ alpha}}$) phases was 1.4 +/- 0.5 min and 14.3 +/- 6.5 min, respectively. The mean elimination half-life, $t_{1/2\text{ beta}}$ was 103.8 +/- 20.2 min. The mean (+/- SD) total body clearance was 14.1 +/- 4.4 ml X kg⁻¹ min⁻¹, and the total apparent volume of distribution ($V_{d\text{ beta}}$) was 2.04 +/- 0.50 l/kg. The short terminal half-life of droperidol does not correlate with the well-known, relatively prolonged duration of its pharmacologic action.