

Does Low-dose Droperidol Increase the Risk of Polymorphic Ventricular Tachycardia or Death in the Surgical Patient?

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ABSTRACT

Background: The Food and Drug Administration issued a black box warning regarding the use of droperidol and the potential for torsade de pointes.

Methods: The primary objective of this retrospective study was to determine if low-dose (0.625 mg) droperidol administration was associated with episodes of torsade de pointes in the general surgical population during the 3-yr period following the reinstatement of droperidol to our institutional formulary.

Results: The authors identified 20,122 surgical patients who received 35,536 doses of droperidol. These patients were cross-matched with an electrocardiogram database and an adverse outcome database. The charts of 858 patients were reviewed, including patients with documentation of prolonged QTc (>440 ms) from March 2007 to February 2011, polymorphic ventricular tachycardia (VT) within 48 h of receiving droperidol, or death within 7 days of receiving droperidol. Twelve surgical patients had VT (n = 4) or death (n = 8) documented within 48 h of droperidol administration. No patients developed polymorphic VT or death due to droperidol administration (n = 0). The eight patients that died were on palliative care. The four patients with documented VT had previous cardiac conditions: two had pre-existing implantable cardiac defibrillators, three had episodes of VT before receiving droperidol, and another had pre-existing hypertrophic obstructive cardiomyopathy.

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What We Already Know about This Topic

- The Food and Drug Administration warns that droperidol may prolong QT intervals and result in ventricular tachycardia, but that warning only applies to approved doses, which are much greater than those used for nausea prophylaxis in anesthesia

What This Article Tells Us That Is New

- In a review of over 20,000 patients receiving over 35,000 doses of droperidol (0.625 mg), no patient developed polymorphic ventricular tachycardia, including over 500 patients with prolonged QT intervals
- These data suggest that ventricular tachycardia induced by droperidol, if it exists, must be rare

The authors found 523 patients with a documented QTc >440 ms before receiving droperidol. No patients developed VT or death as a direct result of droperidol administration.

Conclusions: Our evidence suggests that low-dose droperidol does not increase the incidence of polymorphic VT or death when used to treat postoperative nausea and vomiting in the surgical population.

POSTOPERATIVE nausea and vomiting (PONV) results in an increased length of hospital stay and decreases patient satisfaction. Droperidol, is used as an antiemetic and for treatment of agitation and delirium in critically ill patients.¹ Low-dose droperidol, in the dose range of 0.625–1.25 mg, has been used successfully by anesthesia providers for the treatment and prevention of PONV in millions of patients for over 30 yr.^{2,3} Droperidol acts centrally by antagonizing one of the pathways causing nausea and vomiting.⁴

In December 2001, The U.S. Food and Drug Administration issued a black box warning for droperidol based on safety reports of adverse cardiac events believed to be associated with QTc prolongation and the development of torsades de pointes (TdP), a form of polymorphic ventricular tachycardia (VT).³ Before issuing the warning, there was accumulating evidence of QT prolongation and risk for TdP and the Food and Drug Administration was called upon to review 22 cases of QT prolongation or TdP, including five deaths.⁵ The droperidol package

insert has a starting dose of 2.5 mg; although 18 of the 22 cases were at doses greater than 2.5 mg, 4 of the 22 cases reviewed by the Food and Drug Administration were associated with doses less than 2.5 mg.⁵ Habib and Gran reviewed 10 of these cases of adverse cardiac events or death involving droperidol at doses of 1.25 mg or less. They concluded that a cause-and-effect relationship could not be established due to the presence of possible confounding factors.⁶ The black box warning states “Cases of QT prolongation and/or TdP have been reported in patients receiving droperidol at doses at or below recommended doses,”⁷ with the recommended doses being consistent with what the package insert indicates: 2.5 mg.⁵ Since that time, the primary Food and Drug Administration medical office responsible for droperidol labeling has stated that “the boxed warning really is not about doses of droperidol less than 2.5 mg because the use of droperidol at doses less than 2.5 mg is off label. We do not have data submitted to the agency to make a determination of safety and efficacy at less than 2.5 mg, and we really are not making any statement about the safety or lack of safety of droperidol at those doses.”⁸ Despite this important detail, all use of droperidol fell out of favor after the black box warning was issued, and other antiemetics such as ondansetron and granisetron were used.⁷

In October 2007, a study was released from our institution demonstrating that low-dose droperidol administration does not increase the risk of drug-induced QTc prolongation and TdP in the general surgical population.⁷ As a result of this study, this institution placed low-dose droperidol back on its formulary for its use in preventing and treating PONV. Our aim is to determine the safety of low-dose droperidol in the general surgical population. The primary objective of this retrospective safety study was to determine if low-dose droperidol administration for postoperative nausea increased the incidence of polymorphic VT or death. A secondary objective was to determine if any patients with a previously documented prolonged QTc received droperidol, further resulting in polymorphic VT or death.

Materials and Methods

Following Institutional Review Board approval (Rochester, Minnesota), this retrospective safety study was performed on patients that underwent surgery at Mayo Clinic, Rochester. Droperidol was placed back on the Mayo Clinic Formulary in March of 2008 for its use in the prevention of PONV. Using the electronic Anesthesia Quality Assurance system database (Performance Improvement Database), we identified patients

who underwent surgery at Mayo Clinic, Rochester from March 2008 to February 2011. All patients at Mayo Clinic, Rochester who required anesthesia services for outpatient or inpatient surgeries and procedures were included and entered into the electronic Anesthesia Quality Assurance system. The electronic system became effective in 1998.

Once we identified surgical patients in this time range, the pharmacy database and the anesthesia database were cross-matched to produce a list of 20,122 surgical patients that received 35,536 doses of droperidol. These patients were then cross-matched with both an electrocardiogram database and an adverse outcome database. The electrocardiographic results of all patients who have a 12-lead electrocardiogram or Holter performed at Mayo Clinic, Rochester are entered into the electrocardiogram database. Since 1982 all electrocardiograms have been recorded in electronic format. To identify patients who were at increased risk for developing TdP, we reviewed the charts of patients with prolonged QTc and/or any VT. Because our electrocardiogram database may not distinguish between monomorphic versus polymorphic VT, we cross-matched and reviewed all VT electrocardiograms. Further, to ensure that patients who did not have a 12-lead electrocardiogram performed in the perioperative period who nevertheless developed VT were captured, we used the adverse outcome database to identify patients who died within 7 days of droperidol administration and reviewed these charts.

The result of this database cross-matching produced a list of 858 patients, which included patients with: documentation of any prolonged QTc (>440 ms) at this institution in the time period from March 2007 to February 2011, VT within 48 h of receiving droperidol, or death within 7 days of receiving droperidol. The prolonged QTc may have occurred before or after a droperidol dose was administered. We did not extract when the prolonged QTc occurred, rather, used the presence of prolonged QTc in the patient's record as a way to establish our patient list. Once those patients who experienced either monomorphic or polymorphic VT or death were identified, the following was extrapolated: patient demographics, dates and dosages of all droperidol administrations within 48 h of the events, predrug and postdrug 12-lead electrocardiograms, presence of an internal cardiac defibrillator, and documentation of sudden cardiac arrest or VT. A descriptive analysis was completed on patients found to experience VT or death within the aforementioned timeframes.

A secondary objective was to determine if any patients with a previously documented prolonged QTc received droperidol, further resulting in polymorphic VT or death. In order to accomplish this, we reviewed the most recently documented QTc on 12-lead before the first dose of droperidol.

All general surgical patients from March 2008 to February 2011 who received low-dose droperidol were included in this study. The patients studied required a thorough chart

¹ Food and Drug Administration, Transcript of the Meeting of the Anesthetic and Life Support Drugs Advisory Committee, November 18, 2003, page 64, lines 4–11. Available at: <http://www.fda.gov/ohrms/dockets/ac/03/transcripts/4000T1.DOC>. Accessed August 20, 2012.

review to determine if droperidol was a possible cause for polymorphic VT or death. Chart reviews were done with the electronic medical record (Synthesis, Rochester, MN), and included only patients who had previously provided consent *via* the Institutional Review Board research authorization inquiry. To ensure reliability in our data collection between the four researchers, we examined the first 10 charts together and compared the data for consistency.

Statistical Analysis

Data abstracted from the medical records were entered into an electronic database using the web-based Research Electronic Data Capture (REDCap) system (Version 3.6.7, Vanderbilt University, Nashville, TN). Descriptive analyses were performed using JMP software (Version 9.0, SAS Institute Inc., Cary, NC). Event rates are summarized as the number of events per 10,000 patients with 95% CI calculated using Poisson approximation to the binomial.

Results

From March 2008 to February 2011, 12 out of 20,122 surgical patients had VT ($n = 4$; event rate = 2.0 per 10,000, 95% CI 0.5 to 5.1 per 10,000) or died ($n = 8$; event rate = 4.0 per

10,000, 95% CI 1.7 to 7.8 per 10,000) within 48 h of droperidol administration. There were no patients who clearly developed polymorphic VT or died due to droperidol administration ($n = 0$; event rate = 0.0 per 10,000, 95% CI 0.0 to 1.8 per 10,000). All of the eight patients who died were on palliative care and died of their disease (table 1).

All of the four patients with documented VT had previous cardiac conditions: two had pre-existing internal cardiac defibrillators, three had episodes of VT before receiving droperidol, and another had pre-existing hypertrophic obstructive cardiomyopathy and underwent a septal myectomy (table 2). Interestingly, one patient received 66 doses of droperidol over 27 days during which prolonged QTc was present and did not result in polymorphic VT or death.

Our secondary objective focused on those patients with pre-existing long QTc. We wanted to determine if these patients received droperidol which resulted in polymorphic VT or death. From our data set, a total of 523 patients had a documented QTc >440 ms in the medical record within 1 yr before receiving droperidol, 323 patients did not. These 323 patients had a prolonged QTc documented at some time during the study period, but not specifically 1 yr before droperidol administration. The black box warning on droperidol defines prolonged QTc for men as greater than 440 ms and

Table 1. Death within 48 h of Droperidol Administration

Age (years)	Sex M/F	Predroperidol QTc (ms)	Postdroperidol QTc (ms)	Time after Droperidol until Death (Hours)	Withdrawal of Cares or Palliative Cares (Yes/No)	Comments
85	F	NA	445	48	Yes	History of metastatic colorectal carcinoma, malignant colonic obstruction.
87	F	430	NA	13	Yes	Admitted with small bowel obstruction, subsequent multiorgan system failure.
56	F	541	NA	17	Yes	History of severe alcoholic cirrhosis, with perforated ulcer to anterior pylorus. Biliary peritonitis resulted in renal and liver failure.
88	F	408	NA	48	Yes	History of COPD, anticoagulated for atrial fibrillation. Subsequently developed a large subdural hematoma with significant neurological defect.
47	M	NA	NA	*48	Yes	History of metastatic colon cancer, small bowel obstruction. Several doses of droperidol (25 doses) given in the month before death.
28	M	413	NA	6	Yes	Acute respiratory failure due to aspiration, requiring intubation.
53	M	478	NA	17	Yes	Renal and liver failure secondary to duodenal cancer. Placed on comfort cares 1 day after admission.
65	M	455	NA	10	Yes	Respiratory failure secondary to blastomycosis, pulmonary infection, and multisystem organ failure.

* Patient died at home, time of death not documented, but date available.

COPD = chronic obstructive pulmonary disease; F = female; M = male; NA = not available.

Table 2. Patients with Ventricular Tachycardia within 48 h of Receiving Droperidol

Age (years)	Sex M/F	Predroperidol QTc (ms)	Days Before Droperidol that the QTc was Measured	Dose of Droperidol Given (mg)	Time after Drug to VT, Hours	Comments
46	M	497	1 Day	Not recorded	16 h	H/o VT, cardiomyopathy, Marfans disease, hospitalized for ICD revision. Underlying rhythm of 3rd degree HB, rate 35. ICD alarm review showed: "Nonsustained VT and PVCs > 10 min."
68	M	467	3 Days	0.625 w/in 48 h	9 h	H/o CHF, VT requiring ICD and chronic amiodarone use, CAD s/p CABG, dual chamber pacing, COPD. Admitted for radiofrequency ablation and considered for LVAD or transplant in future. ICD shocked after events of VT the first night after droperidol given.
45	F	495	1 Day	0.625 w/in 48 h	Exact time not clear, droperidol at 0256, VT runs "during the night"	H/o mitral valve prolapse and severe regurgitation with MVR complicated by several short runs of VT before and after droperidol administration. Angiogram and expert consultation revealed cause of these episodes of self-terminating VT to be coronary artery vasospasm due to perioperative inflammation.
15	F	448	1 Day	0.625 w/in 48 h	Exact time not clear, droperidol at 1718 and 1837- 3 beat VT run "during the night" after myectomy	H/o hypertrophic cardiomyopathy s/p myectomy. Had 3 beat run VT the night after surgery after receiving two dosages of droperidol. Also received droperidol day after with no VT. Had an ICD placed as she was at risk for sudden death due to cardiomyopathy.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; F = female; HB = heart block; H/o = history of; ICD = implantable cardiac defibrillator; LVAD = left ventricular assist device; M = male; MVR = mitral valve repair; PVC = premature ventricular contraction; VT = ventricular tachycardia.

women as being greater than 450 ms.³ Of the 523 patients with QTc greater than 440 ms within 1 yr before receiving droperidol, our data revealed that 230 were men and 293 were women. More specifically, in accordance with the black box warning, 249 women had a documented QTc greater than 450 ms. None of these patients developed VT or died following low-dose droperidol administration.

Discussion

To determine drug safety, studies with very large numbers of patients are needed. We identified 20,122 surgical patients who had received 35,536 doses of droperidol. We found no evidence suggesting that low-dose droperidol increases the incidence of polymorphic VT or death when used to treat PONV in the surgical population. Our results are consistent with a recent quantitative system review of 25 trials of low-dose droperidol in 2,957 patients by Schaub *et al.*⁸ They found that prophylactic doses of droperidol less than 1 mg were antiemetic and there were no reports of QT prolongation or cardiac arrhythmia.

The current literature indicates that droperidol is associated with a prolonged QTc interval.^{4,9} The question remains, however, if this prolongation is known to lead to adverse outcomes, particularly polymorphic VT or death. In 2005, White *et al.* studied low-dose droperidol (0.625 mg and 1.25 mg IV), in a random double blinded placebo control study to evaluate the QT interval when used for nausea prophylaxis.¹⁰ They studied 120 patients undergoing outpatient surgery with general anesthetics. These patients were given either 0.625 mg or 1.25 mg of droperidol or saline and their QT intervals were analyzed at intervals up to 2 h after surgery. The study found no statistically significant difference in the QT interval greater than 10% of their baseline in patients receiving droperidol *versus* the saline. The study also found no evidence of droperidol induced QTc prolongation in the immediate postoperative period.¹⁰

Mehta *et al.* conducted a study that was published in 2010 to compare the effects of droperidol and ondansetron on the QT interval in children.¹¹ One hundred and eight children undergoing elective outpatient surgery were randomized to receive droperidol at 20 mcg/kg, ondansetron at

100 mcg/kg, or a saline placebo. There were no differences in QT interval prolongation after treatment with droperidol or ondansetron. Furthermore, there were no dysrhythmias noted. Based on the study's findings, the authors concluded that droperidol and ondansetron are highly unlikely to increase the risk of torsades in healthy pediatric patients.¹¹

We identified a number of limitations with this retrospective safety study, including: the inability to capture brief episodes of polymorphic VT with a 12-lead electrocardiogram, correct diagnosis of the event, or technical issues with how the database extracted its data. To eliminate bias we relied on documented medical provider diagnoses. The VT identified by provider documentation was not captured on 12-lead on any of the four patients who experienced VT. Therefore, we had limited information on these events to review. Nursing documentation did not differentiate between monomorphic or polymorphic VT, only noting that VT was present. Another potential limitation was not identifying patients who had undocumented transient nonfatal or fatal polymorphic VT within 48 h after droperidol administration. A further limitation of this study is the reliability of provider documentation in the electronic medical record, particularly regarding correct documentation of medication administration. There were patients who had droperidol removed from the pharmacy but there was no documentation in the medical record of drug administration. Therefore, we included all patients that had droperidol removed from the pharmacy as opposed to sole documentation on the medication administration record.

We concluded that none of the patients in our study who experienced VT or died within 48 h of droperidol administration could be directly associated with droperidol. All of the patients that died were on palliative care and died of their disease. All of those patients that experienced VT had severe pre-existing cardiac comorbidities. We found 20,122 surgical patients who were exposed to low-dose droperidol with no evidence suggesting that it increases the incidence

of adverse outcomes. Therefore, we concluded that the use of low-dose droperidol for the prevention and treatment of nausea and vomiting in the surgical population is safe when combined with discretionary medical judgement.

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