Does Low-dose Droperidol Administration Increase the Risk of Drug-induced QT Prolongation and Torsade de Pointes in the General Surgical Population?


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

Methods: The primary objective of this retrospective study was to determine whether low-dose droperidol administration increased the incidence of TdP in the general surgical population during a 3-yr time period before and after the Food and Drug Administration black box warning. A random sample of 150 surgical patients during each time interval was selected to estimate the droperidol use for each time period.

Results: During the time period before the black box warning (July 1, 1998 to June 30, 2001), 2,321/139,932 patients (1.66%) had QT prolongation, TdP, or death within 48 h after surgery. We could identify no patients who clearly developed TdP before the black box warning. There was one patient for whom the cause of death could not positively be ruled out as due to TdP. In the time period after the black box warning (July 1, 2002 to June 30, 2005), 2,207 patients (1.46%) had documented QT prolongation, TdP, or death within 48 h after surgery, including only two cases (<0.1%) of TdP. The incidence of droperidol exposure was approximately 12% (exact 95% confidence interval, 7.3–18.3%) before the black box warning and 0% after placement of the black box warning on droperidol. Therefore, we estimate that approximately 16,791 patients (95% confidence interval, 10,173–25,607) were exposed to droperidol. Therefore, we estimate that approximately 16,791 patients (95% confidence interval, 10,173–25,607) were exposed to droperidol, none of whom experienced documented TdP.

Conclusions: This indicates that the Food and Drug Administration black box warning for low dose droperidol is excessive and unnecessary.

DROPERIDOL, a butyrophenone, is most often used as a premedication for anesthesia, treatment for nausea and vomiting after anesthesia, and sedation of agitated patients. The maximum recommended initial dose for prevention or treatment of postoperative nausea and vomiting (PONV) is 2.5 mg intravenous or intramuscular. Additional 1.25-mg doses of droperidol may be administered to achieve desired effect. Droperidol has been used successfully by anesthesiologists for the treatment and prevention of PONV in millions of patients for more than 30 yr. A review of the literature reveals conflicting facts regarding the administration of droperidol and compounding factors that may be associated with the potential for drug-induced long QT syndrome (LQTS).

In December 2001, the US Food and Drug Administration (FDA) issued a black box warning regarding the use of droperidol and the potential for drug-induced QT prolongation and torsade de pointes (TdP). The warning stated that “cases of QTc prolongation and/or TdP have been reported in patients receiving droperidol at doses at or below recommended doses.” The warning was based on 10 reported cases in association with droperidol use (1.25 mg or below) over the approximately 30 yr that droperidol has been available on the market worldwide. Before this warning, 0.625–1.25 mg intravenous droperidol had been accepted widely as a first-line therapy for management of PONV with a 30-yr history of low side effects and high cost-effectiveness. A comparably effective rescue drug for PONV does not currently exist, although promethazine and dimenhydrinate have been used.

After the black box warning on droperidol, 5-hydroxytryptamine type 3 (5-HT₃) antagonists (ondansetron, granisetron, and dolasetron) became the first-line treatment both for prevention and treatment of PONV. Interestingly, these 5-HT₃ antagonists are listed among QT interval–prolonging drugs with possible risk of TdP.* The FDA case reports, MedWatch reports, and data from the manufacturer have been examined, and both literature reviews and editorial comments have suggested the black box warning on droperidol is unwarranted. At this time, no published studies have conclusively related the recommended low-dose droperidol administration used in prevention or treatment of PONV to the development of drug-induced LQTS consisting of either QT prolongation or development of TdP. Because the FDA black box warning was based on case reports, we

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sought to determine the true incidence of TdP associated with droperidol use in a large anesthesia practice.

Materials and Methods

After institutional review board approval (Rochester, Minnesota), we performed a retrospective study of patients who had undergone surgery with general anesthesia or central neuraxial blockade at Mayo Clinic Rochester during the 3-yr time period from July 1, 1998 to June 30, 2001 (before the black box warning) and the 3-yr time period from July 1, 2002 to June 30, 2005 (after the black box warning). These time frames were expected to capture a realistic use of droperidol before the black box warning and the decreased use after the warning.

The primary endpoint for this investigation was the occurrence of TdP within 2 days after surgery. The frequency of TdP was estimated separately for each calendar period and compared between periods using descriptive analysis. The frequency of droperidol use was extrapolated for each time period using data from random sampling.

Using the electronic Anesthesia Quality Assurance system (Performance Improvement Database) database, we identified 139,932 patients who underwent surgery with general anesthesia or central neuraxial blockade at the Mayo Clinic Rochester during the earlier time window and 151,256 patients who underwent surgery during the latter time period. All patients who require anesthesia services are included: Inpatients, outpatients, and all procedures (radiologic imaging, such as magnetic resonance imaging and/or computed axial tomography scanning; bronchoscopy, endoscopy, and other interventional procedures including cardiac catheterizations) at Mayo Clinic Rochester are entered into our electronic Anesthesia Quality Assurance system. The electronic system became effective on November 1, 1988. By merging the anesthesia database patient’s data with an electrocardiogram database, we determined that 2,321 (1.66%) patients in the earlier time period and 2,207 (1.46%) patients in the latter time period had documented QTc prolongation, TdP, or death within 2 days after their surgical procedure (fig. 1). 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, and starting in 1982, the electrocardiograms were recorded in electronic format. The QTc calculation was performed according to the method of Bazett. To identify patients who developed TdP, we reviewed the charts of patients with prolonged QTc and/or any ventricular tachycardia.

Further, to ensure that patients who did not have an electrocardiogram performed in the perioperative period who nevertheless developed TdP were captured, we used a database to identify patients who had a death within 48 h of surgery and reviewed these charts for evidence of TdP.

The charts of these 4,528 patients with documented QTc prolongation, TdP, or death within 2 days after their surgical procedure were reviewed to determine whether the patient had an adverse cardiac event afterward, notably TdP. For all patients who had TdP, a thorough chart review was performed to collect demographic and potential risk factor information, including droperidol use within 2 days of surgery and other drugs or medical conditions known to increase the risk of TdP. A descriptive analysis of the cases of TdP for the time periods before and after the December 2001 black box warning was conducted.

In addition to the aforementioned data, a random sample of 150 surgical patients during each time interval was selected to estimate the droperidol use for each time period (fig. 2). With the sample size of 150 patients, we would be able to estimate the percentage of droperidol use before the black box warning with precision of approximately plus or minus 5% based on the width of the 95% confidence interval (CI). Timing of droperidol administration as well as amount of droperidol given were recorded.
Results

The time period before the black box warning (July 1, 1998 to June 30, 2001) included 2,321 patients (1.66%) who died within 48 h after surgery, experienced TdP, or exhibited QT interval prolongation. We could identify no patients who clearly developed TdP before the black box warning. Of the 456 patients who died within 48 h after surgery in the time period before the black box warning, there was only one patient for whom the cause of death could not positively be ruled out as due to TdP. This patient was a 48-yr-old, obese (104-kg, 165-cm) woman, status-post orthopedic surgery, who was found unresponsive and pulseless in bed. She had received 1.25 mg intravenous droperidol at 11:30 AM in surgery and 4 mg ondansetron at 5:00 PM in the postanesthesia care unit. Her operative and postoperative course was uneventful. She was transferred to the floor. She was evaluated around 9:30 PM and found to be in no distress. She was found at approximately 10 PM to be unresponsive and pulseless. Therefore, this event occurred at least 10 h after her exposure to droperidol. None of her notes indicated TpD. She was resuscitated from asystole to rapid atrial fibrillation with epinephrine and atropine then controlled with amiodarone. After resuscitation, a presumptive diagnosis of pulmonary embolism was made and treated with antifibrinolytics and heparin. A pulmonary embolism was ruled out subsequently by rapid chest computed tomography. Computed tomography of her head revealed diffuse cerebral edema. She remained unresponsive and died 2 days later. The autopsy report listed the immediate cause of death as acute hypoperfusion injury and acute pneumonitis. She did not have a baseline electrocardiogram to identify her QT interval (table 1).

In the time period after the black box warning (July 1, 2002 to June 30, 2005), we identified 2,207 patients (1.46%) who died within 48 h after surgery, experienced TdP, or exhibited QT interval prolongation. In this group, there were two cases of documented TdP (table 1). One patient was a 6-week-old infant who underwent repair of congenital cardiac anomalies and experienced TdP postoperatively. The other patient was a 74-yr-old woman undergoing aortic valve repair. She experienced multiple arrhythmias, including TdP, perioperatively and postoperatively. Neither patient received droperidol; however, they had many other confounding, TdP-predisposing risk factors, such as cardiac surgery.

Other occurrences of TdP were identified. They were excluded for the following reasons: TdP occurring before surgery, TdP occurring more than 48 h postoperatively, and TdP occurring in a setting unrelated to anesthesia.

Table 1. Patients Experiencing Torsade de Pointes

<table>
<thead>
<tr>
<th>Date of Surgery</th>
<th>Preoperative QTc, ms</th>
<th>Postoperative QTc, ms</th>
<th>Other Causes of Long QT</th>
<th>Droperidol Administration, mg</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 28, 2001</td>
<td>No ECG</td>
<td>No ECG</td>
<td>4 mg ondansetron in recovery</td>
<td>1.25 intraoperative</td>
<td>48-yr-old female orthopedic surgery patient found unresponsive and pulseless in bed. Pulmonary embolism ruled out. Cardiac rhythm before event unknown.</td>
</tr>
<tr>
<td>December 23, 2002</td>
<td>No ECG</td>
<td>413, 419, 542</td>
<td>Congenital cardiac anomalies</td>
<td>None</td>
<td>6-wk-old patient with failure to thrive, hypoplastic aortic arch, and juxtaductal coarctation repair. NSR and stable hemodynamics off-pump. Postoperative day 1, two episodes of TdP treated successfully with magnesium, propranolol, and digoxin.</td>
</tr>
</tbody>
</table>

Other occurrences of torsade de pointes (TdP) were identified. They were excluded for the following reasons: TdP occurring before surgery, TdP occurring more than 48 h postoperatively, and TdP occurring in a setting unrelated to anesthesia.

ECG = electrocardiogram; NSR = normal sinus rhythm.
fore surgery or droperidol exposure \( (n = 1) \), TdP occurring more than 48 h postoperatively \( (n = 2) \), and TdP occurring in a setting unrelated to anesthesia \( (n = 3) \). None of the excluded patients received droperidol within 48 h before their event.

Based on a random sampling of 150 surgical cases, the incidence of droperidol exposure at our institution during the time period before the black box warning was estimated to be 12% (exact 95% CI, 7.3–18.3%). Therefore, of 139,932 patients in the time period before the black box warning, we estimate that approximately 16,791 (95% CI, 10,173–25,607) patients were exposed to droperidol, none of whom experienced documented TdP. Using the conservative estimate of 10,173 exposed patients, the upper bound (based on a 95% CI) for the rate of TdP in patients receiving droperidol is 3.6 per 10,000. The incidence of droperidol exposure approached 0%, with none of the 150 randomly sampled surgical cases associated with droperidol use after the placement of the black box warning on droperidol.

Discussion

We found no evidence supporting the black box warning placed on droperidol by the FDA when used to treat PONV in the surgical population. Droperidol use as an antiemetic in the perioperative period decreased from 12% to 0% after the December 2001 FDA black box warning for droperidol because of concerns regarding drug-induced LQTS. There was no change in the incidence of TdP with the commonly used low-dose droperidol versus no droperidol use in a large number of surgical patients. This indicates that the incidence of TdP is at most 1 in 16,791 (95% CI, 10,173–25,607) droperidol exposures, with that 1 patient also having received 1.25 mg droperidol 10 h before the event and having received ondansetron, another implicated drug for possible drug-induced TdP 5 h before the event. Given the short half-life of droperidol, it is unlikely that droperidol contributed to this patient’s dysrhythmia. This indicates that the FDA black box warning is excessive and unnecessary for low-dose droperidol therapy. The data suggest that the guidelines initiated by the FDA for mandatory electrocardiographic screening before administration of droperidol are also unnecessary for patient safety.

There are many confounding factors that can be associated with both QTc prolongation and TdP. Approximately 1 in 3,000 persons have congenital LQTS caused chiefly by genetic mutations in cardiac potassium and sodium channels. For acquired LQTS, there is a long list of drugs and medical conditions that are reported to prolong the QT interval and predispose patients to TdP.\(^1\)\(^-\)\(^9\) Most of these drugs precipitate drug-induced LQTS by inhibiting cardiac potassium channels, particularly the LQT2-associated 1K\(r\) potassium channel encoded by \(\text{KCNH}2\). Among these drugs, antiarrhythmic agents such as quinidine, sotalol, dofetilide, and ibutilide have the greatest potential to induce fatal TdP. There are nine structurally unrelated drugs that were marketed in the United States or elsewhere for a range of cardiovascular indications that have been removed from the market or had their availability severely restricted because of this rare disastrous effect.\(^9\) Along with droperidol, these drugs include terfenadine, astemizole, grepafloxacin, terodiline, lidoflazine, sertindole, levomethadyl, and cisapride. Many antipsychotic and antiemetic drugs, including the 5-HT\(_3\) antagonists, are listed among QT interval–prolonging drugs with possible risk of TdP.\(^5\)\(^-\)\(^10\) Curiously, droperidol is the only antiemetic that has received the black box warning.

Recently, it has been suggested that QT prolongation is not the significant effect per se for TdP, but rather the risk factor is transmural dispersion of repolarization that is manifested by a widened T wave.\(^11\) Whyte et al.\(^12\) has suggested that the time interval from the peak to the end of the T wave would be a good measure of transmural dispersion of repolarization. Whyte et al.\(^12\) also has pointed out that QTc prolongation is a poor predictor of the actual risk of TdP, because 40% of patients congenital QT prolongation are asymptomatic at the time of diagnosis, and there are many drugs that are known to prolong the QT interval but have not been shown to induce TdP.

There have been several well-controlled, randomized, comparative clinical trials where droperidol has been demonstrated to be as safe and effective as the more costly 5-HT\(_3\) antagonists.\(^13\)\(^-\)\(^15\) One large-scale study, involving more than 2,000 outpatients, conducted by the manufacturer of ondansetron (Zofran\(^\text{®}\); Glaxo Smith Kline, Research Triangle Park, NC), did not find any safety or efficacy advantages of 4 mg intravenous ondansetron over 0.625 or 1.25 mg intravenous droperidol.\(^14\) In a review article by Roden\(^16\) on the subject of drug-induced LQTS, he noted that “Rare, poorly understood side effects occur with many highly-effective drugs, and the withdrawal of these medications from the market probably harm more patients than it helps.”

In high doses, droperidol certainly can cause severe dysrhythmias.\(^16\)\(^-\)\(^17\) Many of the adverse cases were found within the FDA database, and such cases undoubtedly caught the attention of the FDA officials. However, such large doses of droperidol are not needed to prevent emesis in surgical patients. In 2000, Hill et al.\(^15\) performed a randomized, double-blind, placebo-controlled, multicenter study including 50 institutions in North America, where patients were randomized to one of four intravenous treatments: 4 mg ondansetron, 0.625 mg droperidol, 1.25 mg droperidol, or placebo (normal saline). They found that the use of 1.25 mg intravenous droperidol was associated with greater effectiveness, lower costs, and similar patient satisfaction compared
with 0.625 mg intravenous droperidol and 4 mg intravenous ondansetron.

But is droperidol given at the usual antiemetic doses “QT safe”? Our data would certainly suggest that it is. White et al.\textsuperscript{18} performed a randomized, double-blind, placebo-controlled trial to evaluate the intraoperative and postoperative effects of low-dose droperidol (0.625 and 1.25 mg intravenous) on the QT interval when used for antiemetic prophylaxis during a standardized general anesthetic. They found that the 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 QT interval compared with saline. Further, there was no evidence of any droperidol-induced QT prolongation immediately after surgery.

There has been a suggestion that there should be a threshold dose of droperidol, such as 5 or 10 mg, beyond which the stipulations of the black box warning would apply.\textsuperscript{16} Chan et al.\textsuperscript{17} performed a prospective trial where 400 patients scheduled to undergo laparoscopic gynecologic surgery were assigned randomly to receive intravenous saline, 4 mg intravenous ondansetron, 1.25 mg intravenous droperidol, or a combination of 1.25 mg intravenous droperidol and 4 mg intravenous ondansetron 5 min before induction of anesthesia. They used a standardized anesthetic technique and postoperative analgesic regimen. They noted a modest increase in the QT interval after administration of ondansetron, droperidol, or their combination that resolved by 2–3 h after drug administration. There was no difference between drugs in change of QT interval. They concluded that a combination of 4 mg ondansetron and 1.25 mg droperidol produced an additive effect for preventing PONV after laparoscopic gynecologic surgery.

A panel of experts was convened in 2002 to develop consensus guidelines for the management of PONV.\textsuperscript{20} They stated, “If it were not for the ‘black-box’ warning, droperidol would have been the panel’s overwhelming first choice for PONV prophylaxis.” They recommended the use of antiemetics from different classes for the treatment of established PONV in patients who failed prophylaxis. In the absence of available data, this recommendation was based on expert opinion. In a prospective study, patients were randomly assigned to receive 4 mg ondansetron, 1.25 mg droperidol, 0.625 mg droperidol, or placebo.\textsuperscript{2} Patients who developed PONV received rescue antiemetics at the discretion of the attending anesthesiologist in the postanesthesia care unit. The antiemetics used for rescue therapy were 4 mg ondansetron, 0.625–1.25 mg droperidol, 10 mg metoclopramide, 6.25–25 mg promethazine, and 25–50 mg dimenhydrinate mg. They found that among those patients who failed prophylaxis with 4 mg ondansetron, the complete response rate was significantly higher (P = 0.02) after rescue with 6.25–25 mg promethazine (78%) than after rescue with 4 mg ondansetron (46%). Further, for those patients who failed prophylaxis with 0.625 and 1.25 mg droperidol, the complete response rate was significantly higher after rescue with 6.25–25 mg promethazine (77%; P = 0.02) and 25–50 mg dimenhydrinate (78%; P = 0.04) than after rescue with 0.625–1.25 mg droperidol (56%). These results suggest that drugs acting at a different receptor site might be more efficacious for the treatment of established PONV for patients who have failed prophylaxis with an antiemetic agent compared with a repeat dose of the same agent used for prophylaxis. This observation suggests that it would be beneficial to have droperidol as a rescue therapy.

A potential weakness of this study was the difficulty of capturing TdP with the standard 12-lead electrocardiogram due to the brevity of the cardiac rhythm. For this reason, we were forced to rely on notation in the patient records by the physician to provide a diagnosis after the cardiac event had occurred. In addition, not all patients undergoing surgery had an electrocardiogram preoperatively. By capturing patients who died within 48 h after surgery, we expected to identify those with fatal TdP. It is conceivable that a patient could have had transient, nonfatal TdP, and this was not noted in the record and therefore not captured in our study. Further, in the period before the black box warning, the event rate for documented QTc prolongation, TdP, or death within 2 days after their surgical procedure was 1.66% (2,321 of 139,932). After the black box warning, and the virtual elimination of droperidol use, this event rate was reduced to 1.46% (2,207 of 151,256). This relatively small 0.2% absolute reduction (approximately 12% relative risk reduction) was statistically different from zero (P < 0.001). Although this event rate was not driven by TdP events, it was hopefully due to practice improvements because the rate of death improved from 456 (0.33%) before the black box warning to 425 (0.28%) after the black box warning (P = 0.025). A final potential weakness of our study was the use of a sample population versus the entire population to estimate the frequency of droperidol use. This limitation is inherent to retrospective studies, because of the vast number of patients required to identify the TdP cases and the fact that use of droperidol was not available in the database.

The findings of our study indicate that despite nearly 17,000 patient exposures to droperidol before the FDA warning, no patient experienced documented TdP. Therefore, our data suggests that droperidol’s black box warning is excessive and unnecessary and that the guidelines initiated by the FDA for mandatory electrocardiographic screening before administration of low-dose droperidol are likely to have a negligible effect on patient safety.
References