

The Use of Droperidol in Anesthesia Care

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At several hospitals in California, Department of Health Care Services inspections required under Medicare and Medicaid “conditions of participation” have resulted in findings of non-compliance related to the use of selected drugs with FDA-mandated boxed warnings (“black box warnings”) in their package labeling. Medications implicated included droperidol. At one institution, a finding of “immediate jeopardy”—the highest level of non-compliance—was cited in relation to droperidol use. Many facilities now have removed droperidol from their formularies in order to avoid such regulatory penalties and any accompanying fines. The propriety of the FDA boxed warning for droperidol has been challenged for years, as is well documented in the medical literature. The boxed warning recommends limiting the use of droperidol to patients who fail to respond to other antiemetics, and it states that a pretreatment 12-lead ECG analysis should occur, followed by continuous ECG monitoring for two to three hours after administration out of concern for serious dysrhythmias. Although institutions in other parts of the country have been affected by the droperidol FDA boxed warning, the phenomenon of state inspectors citing the boxed warning’s recommendations as regulatory mandates seems to be unique to California.

Subsequently, CSA representatives communicated with state officials on this matter, and in November 2007 the California Department of Public Health issued an All Facilities Letter to acute care hospitals regarding FDA boxed warnings. This letter “acknowledges that there may be occasions when a facility has the need to use medications in a manner that is not consistent with manufacturer’s specifications, including those with boxed warnings. In those occurrences, documented evidence should be present of a deliberative, evidence-based process by your medical and pharmacy staff and appropriate hospital committees that support such use while ensuring patient safety.” Subsequently some institutions have adopted policies in accordance with this acknowledgment, allowing the safe use of droperidol in selected settings while not fully adhering to the boxed warning specifications.

Postoperative nausea and vomiting is a significant cause of patient suffering, and droperidol is an important component of multimodal antiemetic therapy. Regarding the FDA boxed warning for droperidol, the Society for Ambulatory Anesthesia’s guidelines for management of PONV cite “considerable concern about the quality and quantity of evidence and the validity of the FDA conclusion. If it were not for the black-box warning, droperidol would have been the panel’s overwhelming first choice for PONV prophylaxis.” Despite the warning, droperidol is an essential part of the algorithm for management of PONV in the SAMBA guidelines.

Droperidol (cont'd)

The cautionary information in the FDA boxed warning and package insert for droperidol should be noted, but evidence for concern regarding serious dysrhythmias with *low-dose* droperidol is lacking. Anesthesiologists should be able to manage PONV unfettered by regulatory mandates that lack a sound scientific basis, and droperidol should be available as an important tool for alleviating patient suffering.

In September, the CSA Board of Directors approved a sample policy template on the use of droperidol in anesthesia care with the intent to provide information that may assist anesthesiologists in drafting institutional policies related to droperidol use. This information is detailed and extensive; policies drafted should conform to the standards and needs of the specific institution.

Sample Policy Template for the Use of Droperidol in Anesthesia Care

Purpose

The purpose of this policy is to describe appropriate use of droperidol for the prevention and treatment of nausea and vomiting in patients having anesthesia for surgical or diagnostic procedures and to document a deliberative, evidence-based process supporting such use while ensuring patient safety.

Background

Droperidol is an injectable butyrophenone medication indicated for the prevention and treatment of nausea and vomiting associated with surgical and diagnostic procedures. Postoperative nausea and vomiting is a significant source of patient suffering, with an incidence of 20-30% after surgery, and it is a common reason for delayed discharge, unplanned admission after outpatient surgery, and increased health care costs.¹ Droperidol is widely recognized as an essential component of the management of PONV, with a long history of safe, effective, and cost-effective use.^{2,3} The most recent Society for Ambulatory Anesthesia Guidelines for the Management of Postoperative Nausea and Vomiting list droperidol among the recommended agents for first-line therapy for prevention and treatment of PONV. These guidelines describe a multimodal therapy approach that utilizes droperidol and several other classes of antiemetic drugs for patients at increased risk for PONV *or* who fail single-drug therapy. Other popular agents such as promethazine and prochlorperazine were considered second-line therapy for preventing PONV due to lack of evidence for their effectiveness. Droperidol is also one of the most cost-effective agents used in PONV therapy. Without the availability of droperidol, management of PONV would be suboptimal, and few antiemetics have a long, established safety record comparable to that of droperidol.

Droperidol (cont'd)

Over more than 35 years, hundreds of millions of doses of droperidol have been given for prevention and treatment of PONV. Much higher doses than are used in the United States for PONV were administered for decades as a part of neurolept anesthesia without any reported cases of serious dysrhythmias. Potential side effects of droperidol include sedation, extrapyramidal reactions, hypotension, and cardiac conduction effects, including prolongation of the QT interval. Recent concerns regarding the safety of droperidol involve the risk for torsades de pointes, a serious ventricular dysrhythmia. Prolongation of the QT interval has been implicated in the development of torsades de pointes. On the other hand, some experts suggest that increased transmural dispersion of repolarization is the critical risk factor producing susceptibility to torsades de pointes, not QT prolongation, which itself is a poor predictor of the risk of torsades de pointes.⁴ Since its approval for use more than 35 years ago, droperidol has been known to cause a dose-dependent prolongation of the QT interval. Nevertheless, it is generally considered to be safe and well tolerated when given at *low doses* for the management of PONV.⁵ Many other medications given to patients under anesthesia care are known also to cause QT prolongation, such as inhaled anesthetics, propofol, thiopental, succinylcholine, and neuromuscular blocker antagonists. In addition, most currently available antiemetics also cause QT prolongation, including phenothiazines, antihistamines, and 5HT-3 antagonists such as ondansetron.⁶ Hypothermia and the duration of general anesthesia are also associated with QT prolongation.

In patients under general anesthesia, QT prolongation with droperidol is equivalent to that seen with saline placebo, with a prolongation of 15 ± 40 ms seen with 0.625 mg droperidol, peaking 3-6 minutes after administration, similar to 12 ± 35 ms QT prolongation with saline. (Maximum peak QT prolongation was 120 ms with droperidol vs. 58 ms with saline.) These differences were present on arrival to PACU but not one hour after arrival.⁷ However, there are rare patients with congenital long QT syndrome, and some patients may be predisposed to drug-induced QT prolongation.⁸

A study of postoperative patients treated in the recovery room for nausea and vomiting showed a maximal QT prolongation of 17 ± 9 ms at 2 minutes after 0.75 mg droperidol and prolongation of 20 ± 13 ms at 3 minutes after 4 mg ondansetron. Prior to antiemetic dosing, 21% of patients had a prolonged QT interval, and this correlated significantly with lower body temperature and longer duration of anesthesia. The drugs did not differ in extent of QT prolongation.⁹

Another study showed a 2.7-3.5% QT prolongation at 5 minutes after pre-induction injection of treatment medications, equal to 11.3 ± 24.3 ms with 1.25 mg droperidol alone, 9.9 ± 34.7 ms with 4 mg ondansetron alone, and

Droperidol (cont'd)

12.5 ± 36.8 ms with a combination of both drugs.¹⁰ No additive effect on QT prolongation occurred when combining droperidol with ondansetron. There does not appear to be any evidence that 5-HT₃ antagonists in clinical use are any safer than droperidol with regard to QT prolongation or dysrhythmia.⁵

The rapid onset and short duration of effect of droperidol on QT interval should inform decisions regarding the monitoring necessary after its administration. Many factors contribute to the post-anesthesia QT interval; determination of a properly corrected QT interval can be difficult; and even if QT prolongation is related to development of dysrhythmia, it is still a surrogate marker for the concerning complication of torsades de pointes.¹¹ On the other hand, 12-lead electrocardiography is not necessary to detect the onset of such a serious dysrhythmia. Overall, the available evidence in the medical literature does not show an association between low-dose droperidol administration and ventricular dysrhythmia.

The FDA Boxed Warning

In 2001, the FDA issued a “black box” warning found in the droperidol package insert, restricting the use of the drug and recommending specific electrocardiographic monitoring because of alleged increased risk of serious cardiac dysrhythmias. The FDA issued this boxed warning without prior input from its expert advisory panel, which then convened in 2003 to provide advice and recommendations regarding the assessments and management of risk related to QT prolongation by droperidol.” The members of this advisory committee expressed that the boxed warning “is unwarranted for antiemetic doses of droperidol and argued that the warning effectively removed one of the most efficacious drugs for the management of PONV.”¹⁰

The FDA decision to issue the boxed warning was based on data from adverse event reports and a few European studies. Among 277 adverse events reported, many were duplicate reports, leaving 65 individual cases. Of these, 10 cases involved serious cardiovascular events in patients who received usual antiemetic doses of 1.25 mg droperidol or less. In many cases, several concomitant drugs known to cause QT prolongation were given, and confounding factors make it impossible to establish cause of the cardiac events. None was seen clearly to be caused by droperidol. Of eleven cases of torsades de pointes (one of whom received 600 mg droperidol), only one occurred in a patient taking 0.625 mg droperidol, but that patient also was admitted with cardiovascular complications and was receiving amiodarone, hydrochlorothiazide, and simvastatin.

The timing of the boxed warning’s issuing and the source of the data behind it have been questioned. After 30 years of post-marketing experience, the “black

Droperidol (cont'd)

box” warning was issued in 2001, at a time when a coincidental shortage of prochlorperazine combined to result in a shift of the antiemetic market share from droperidol to ondansetron.⁵ In addition, the reports were entered between 1997 and 2001, but some of the cases reported occurred in the 1980s. Strangely, 71 of the adverse events, including 55 of the deaths and nine of the eleven cases of torsades de pointes, were reported on a single day, possibly all by one source.¹²

The studies cited as evidence⁵ supporting the boxed warning included a German study of 40 surgical patients receiving various doses of droperidol, the lowest being 0.1 mg/kg, approximately 10 times the typical dosing in the United States. A dose-dependent QT prolongation was observed for 10 minutes. A British study of 495 patients observed a prolonged QT interval in 8% of psychiatric patients receiving 2.5-5 mg po droperidol. Many patients were taking other psychotropic medications. A French case report was also cited. In this case a woman developed torsades de pointes after receiving 12.5 mg IV droperidol. The case report also describes ECG changes observed over 10 minutes in patients who received 0.25 mg/kg droperidol preoperatively, 25 times the typical dose in the United States. Seventy percent of the patients had QT prolongation averaging 35.5 ms.

In response to the FDA boxed warning, the incidence of droperidol exposure at the Mayo Clinic Rochester changed from 12% before the boxed warning was issued to 0% after the boxed warning appeared. A recent report evaluated the incidence of cardiac death and torsades de pointes in the first two postoperative days in 140,000 patients during droperidol use compared to 151,000 patients after droperidol was withdrawn from the Mayo Clinic practice. During droperidol use, no documented episode of torsades de pointes occurred.¹³ One death occurred where torsades de pointes could not be positively ruled out. After withdrawal of droperidol, two documented cases of torsades de pointes occurred. The authors concluded that the FDA black box warning is excessive and unnecessary.¹³ An accompanying editorial stated that the warning itself is still justified but also that the FDA should reconsider and lessen the warning on droperidol.¹⁴ These papers add to an extensive body of literature questioning the clinical validity of the FDA’s boxed warning on droperidol.^{5,6,15} As stated by one expert regarding the droperidol boxed warning, “Many believe that this warning was unjustified given the efficacy of droperidol as an antiemetic, the lack of published evidence of droperidol-induced arrhythmias during decades of use, and the absence of overt toxicity when administered at low doses. On the other hand, a ‘precaution principle approach’ was justified by the known dose-dependent QT interval prolongation and risks of torsade de pointes at the high doses of droperidol used in psychiatry.”¹³

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The Society for Ambulatory Anesthesia's guidelines for management of PONV cite "considerable concern about the quality and quantity of evidence and the validity of the FDA conclusion," and state that "if it were not for the black-box warning, droperidol would have been the panel's overwhelming first choice for PONV prophylaxis." A recent editorial critical of the droperidol boxed warning asserts that "although a warning would have been appropriate, the current black box warning is excessive. Furthermore, the manufacturer was unwilling to supply the FDA with data to support a labeling indicating droperidol for treatment and prophylaxis of PONV at doses < 2.5 mg, even though such a labeling change could be supported entirely from the published literature without additional studies."¹⁶ Even the "con" editorial offered in counterpoint to this one states that "the black box warning should be brought into line with the evidence, the regulatory guidelines, and the longstanding safety history of low dose droperidol by adding the following concluding sentence: 'Doses of INAPSINE below 2.5 mg are considered off-label. The FDA has no position on the safety or efficacy of doses below 2.5 mg.'¹⁷

The cautionary information in the FDA boxed warning and package insert for droperidol should be taken seriously. Droperidol can cause a short-lived, dose-dependent prolongation of the QT interval, and rarely a patient may be sensitive to drug-induced QT prolongation, but evidence for concern regarding serious dysrhythmias with low-dose droperidol is weak. Given the clear effectiveness of droperidol for management of PONV, the magnitude of suffering patients experience with PONV that droperidol helps to alleviate, the dearth of suitable replacements for droperidol in a multimodal regimen for PONV, the long history of safe clinical use of droperidol, the paucity of data in the medical literature to substantiate concerns regarding serious dysrhythmias with low-dose droperidol, and the likelihood that alternative agents may be equally or more likely to produce serious complications, it is desirable to make droperidol available as part of a multimodal approach to the management of PONV.

(The following use criteria should be adapted to the form of the institution's policy conventions. The clinical decisions involved should be carefully considered as part of a deliberative, evidence-based process.)

Restricted Formulary Use Criteria should include:

1. **Areas where droperidol may be administered:** Specific to the institution.
2. **Exclusion criteria:** Droperidol should not be given to patients known to have significantly reduced ventricular systolic function or prolonged QT interval.
3. **Monitoring of patients:** Every patient under anesthesia care has continuous ECG monitoring throughout the procedure. In the post-anesthesia care unit, every patient is monitored for circulatory function and the detection of

Droperidol (cont'd)

dysrhythmia by electrocardiography and/or pulse oximetry. In patients receiving droperidol, the anesthesiologist shall determine the duration of monitoring from the time of administration.

4. **Droperidol administration:** Patients who receive anesthesia care may be given droperidol for the prevention or treatment of nausea and vomiting if they are identified as either a) being at risk of developing nausea and vomiting or b) experiencing nausea or vomiting after having received an alternative antiemetic.
5. **Precautions:** Patients undergoing anesthesia care may receive other medications that cause QT prolongation. Although the effect of droperidol may be short-lived and effects of multiple medications on QT interval may not necessarily be additive, clinicians should consider the possibility that other drugs may contribute to QT prolongation.

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