Food and Drug Administration Black Box Warning on the Perioperative Use of Droperidol: A Review of the Cases

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In a recent Editorial (1), it was suggested that the use of small-dose droperidol has been a highly cost-effective antiemetic for over 30 years. Droperidol, 0.625–1.25 mg IV, has been widely accepted as a first-line therapy for the management of postoperative nausea and vomiting (PONV) (2,3). The decision by the Food and Drug Administration (FDA) to issue a "black box" warning regarding the use of droperidol for the treatment and/or prevention of PONV has been challenged by many anesthesiologists (4).

Under the Freedom of Information Act, we requested information about the cases on which the FDA warning was based. In response, we received data contained in the adverse event reporting system: a computerized database that contains a summary of all adverse events reported to the FDA. There were 273 cases reported to the FDA over the period from November 1, 1997 until January 2, 2002. This information has been previously presented (5). After reviewing the database, we requested copies of the individual case reports (MedWatch forms) in which cardiac adverse events were reported after the use of droperidol at doses of 1.25 mg or less. These forms contain the information voluntarily submitted to the FDA or to the drug manufacturer by consumers or health care professionals. The reporting person determined whether droperidol was the primary or secondary suspect. The content of these forms represents ALL the information that the FDA has about the reported cases. The information extracted from the MedWatch forms is presented in Table 1.

Discussion

We reported the 10 cases in the FDA database in which serious cardiovascular events were possibly related to the administration of droperidol at doses of 1.25 mg or less. A review of these case reports shows that there are several confounding factors that make it impossible to establish the precise cause of the adverse cardiac events. For example, Patient 1 received cyclobenzaprine, a centrally acting muscle relaxant, in combination with fluoxetine for the treatment of fibromyalgia and depression. Cyclobenzaprine is structurally related to tricyclic antidepressants (TCAs) and can cause arrhythmias similar to those induced by the TCAs. Fluoxetine is a known inhibitor of several cytochrome P450 isoenzymes and is likely to inhibit the hepatic metabolism of cyclobenzaprine (6). Furthermore, this patient's baseline electrocardiogram (ECG) demonstrated a prolonged QTc, almost of identical length to that found in the ECG immediately after the event. The fact that the event occurred 150 minutes AFTER an IV injection makes it extremely unlikely that the event was related to the antiemetic drug.

Patient 2 developed ventricular tachycardia 2 minutes after the administration of droperidol and dolasetron. This patient also received ondansetron intraoperatively for PONV prophylaxis. All the 5 HT_3 receptor antagonists can prolong the QT interval and can produce arrhythmias, according to the package inserts of these drugs (1). Arrhythmias have been reported after the administration of ondansetron (7). Sevoflurane and isoflurane were also shown to prolong the QT interval (8,9).

Patient 7 had a history of significant arrhythmias. It is also likely that Patient 9 was developing a cardiac event prior to the administration of droperidol. Other confounding factors, such as cardiac disease, alcoholism, general anesthesia, and the administration of several other drugs with proarrhythmic potential, can be found in the remaining cases. In some of the cases there is also very little information available making it difficult to establish a direct cause-and-effect relationship.

It is estimated that over 11 million ampoules of droperidol were sold in the United States in 2001 (personal communication from manufacturers of droperidol). Possible cardiac events and torsade or

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Table 1. Cases Reported to the Food and Drug Administration of Serious Cardiac Adverse Events or Death Associated with Droperidol at Doses of 1.25 mg or Less

Case (Age, Sex)	Medical history	Regular medications	Presentation	Dose (IV)	Timing prior to CVS event	Other concomitant drugs	Cardiovascular effects	Outcome
1. 59, F*	Hypertension, fibromyalgia, depression	Amlodipine, cyclobenzaprine, diclofenac, fluoxetine, triamterene/ hydrochlorothiazide	Elective tendon Achilles surgery	0.625 mg (45 min preoperatively)	150 min	Metoclopramide, midazolam, propofol, fentanyl, nitrous oxide, isoflurane, atracurium, ketorolac, lidocaine, bupivacaine	Polymorphic VT, TdP, VF (happened intraoperatively)	PH
2. 53, M*	PONV, hepatitis A, migraines, renal and ureteric calculi	N/A	Cystoscopy, stent placement, percutaneous nephrolithotomy	0.625 mg (PACU)	2 min	Dolasetron, propofol, lidocaine, fentanyl, vecuronium, ketorolac, ondansetron, ephedrine, glycopyrolate, neostigmine, nitrous oxide, sevoflurane	VT	PH
3. 53, M**	CABG and MVR (9 mo before the event), elevated bilirubin, AST and ALT	Coumadin, amiodarone, digoxin, frusemide	Admitted to the ER, reason not clear, nausea and vomiting for 5 days	0.625 mg (5 doses)	N/A	N/A	Asystolic arrest	D
4. 35, F**	Recurrent pancreatitis, alcoholism, elevated amylase, and lipase	Antihistamine, paracetamol, aspirin, diazepam	Admitted to the ER with abdominal pain, nausea, vomiting, and severe anxiety	0.75 mg	10 min	Chlordiazepoxide, diazepam, antihistamine, antitussive	Bradyarrhythmia, VF	PH/PI
5. 60, F**	Alcoholism	Omeprazole, sucralfate, estrogen, progesterone	Laparoscopic cholecystectomy	1.25 mg, at induction	N/A	Midazolam, cefotetan disodium, suxamethonium, D-tubocurarine, fentanyl, glycopyrolate	Hypertension, MI, bigeminy (surgery cancelled)	—
6. 66, M**	N/A	N/A	N/A	1.25 mg	30 min	Phenytoin	Hypotension, bradycardia, extrasystoles, VT	LT
7. 22, F**	Palpitation, tachycardia, sick sinus syndrome, previous sinus ablation and single chamber pacemaker insertion, adverse reactions to many drugs	N/A	Pacemaker insertion; the patient had syncope, intermittent hypotension, and apnea with two previous pacemakers	0.625 mg	20 min	Ofloxacin, ibuprofen, diphenhydramine	Hypotension, absent pulse, respiratory arrest	LT PH
8. 63, F**	Hypertension	N/A	Colonic surgery	0.625 mg	N/A	N/A	Congestive cardiac failure, dyspnea, tachycardia	PH
9. Age-N/A, M**	Chest pains since 1 yr but negative workup, palpitations the evening before surgery, suicidal ideation	N/A	Radical nephrectomy	1.25 mg	50 min	Epidural (T8 level) infusion of bupivacaine 0.05% with morphine 100 mg/mL at 14 mL/h	VF, cardiac arrest, hypoxic brain damage	D
10. 49, F**	N/A	N/A	Breast implants (procedure was supposed to be done in a plastic surgeon's office, but aborted following the event)	1.25 mg (given for sedation)	N/A	Metoclopramide, ranitidine	Bradycardia, sinus arrest	PH (24 h)

Droperidol was judged as the primary suspect (**) or secondary suspect (*) for the above cases.

M = male; F = female; D = death; VF = ventricular fibrillation; VT = ventricular tachycardia; TdP = torsade de pointes; MI = myocardial infarction; N/A = information not available; PH = prolonged hospitalization; PI = permanent brain injury; LT = life-threatening; ER = emergency room; CABG = coronary artery bypass graft; MVR = mitral valve replacement; PONV = postoperative nausea and vomiting; CVS = cardiovascular; AST = aspartate aminotransferase; ALT = alanine aminotransferase; PACU = postanesthetic care unit.

Further comments:

1. Case 1: Baseline electrocardiogram (ECG) showed a prolonged QTc of 497 ms. An ECG immediately after cardioversion for VF showed QTc at 500 ms. On postoperative day 1 QT was 440 msec. Cyclobenzaprine was stopped after this event.
2. Case 2: Dolasetron was given in PACU 1 min after droperidol; ondansetron was given during surgery. An ECG after the event showed sinus rhythm, intraventricular conduction delay, flattened T wave and QTc of 441 ms. An ECG performed the following day was reported as normal.
3. Case 6: Only other information available: Serum potassium: 3.3 mmol/L, serum magnesium: 1.4 mg/dL, Phenytoin level: 2.4 μg/mL.
4. Case 7: The patient's physician reported that the patient had previous significant adverse reactions to the following medications: metoprolol, disopyramide, flecainide, codeine, morphine, cephalexin, vancomycin.
5. Case 9: On postoperative day 1, the patient became dizzy and nauseous while sitting in a chair. He was placed in bed and given droperidol 1.25 mg. Thirty-five minutes later he became drowsy, followed by shallow breathing and VF after 15 min. He was resuscitated but suffered hypoxic brain damage and died 3 days later.

prolonged QT occurred in 74 and 17 cases respectively of the 273 cases reported to the FDA (5). Assuming that sales of droperidol remained constant over the 4 years during which these adverse events were reported to the FDA, the incidence of cardiac events and torsade/prolonged QT would be 74:11 million and 17:11 million, respectively. It is, however, to be noted that some of the cases reported to the FDA were from non-US sources, so the true incidence in the United States is probably lower. It is also of note that MedWatch reporting is voluntary, and hence the true incidence may not be known. After the FDA "black box" warning, the sales of droperidol decreased by 10-fold during 2002 compared with 2001 (personal communication from manufacturers of droperidol).

We conclude that in none of the cases in which arrhythmias occurred after small doses of droperidol (1.25 mg or less) was there evidence of a cause-and-effect relationship.

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