The Effect of the FDA Warning on the Use of Droperidol by U.S. Emergency Physicians

John R. Richards, M.D.
Steven J. Weiss, M.D.
Stephen W. Bretz, M.D.
Aaron B. Schneir, M.D.
Dawna Rinetti
Robert W. Derlet, M.D.

Division of Emergency Medicine (JRR, SJW, DR, RWD), University of California, Davis Medical Center Sacramento, California

Department of Emergency Medicine (SWB), San Francisco General Hospital San Francisco, California

Department of Emergency Medicine (ABS), Division of Medical Toxicology University of California, San Diego Medical Center San Diego Division, California Poison Control System San Diego, California

Address for reprints:
John R. Richards, M.D.
Division of Emergency Medicine
2315 Stockton Boulevard
Sacramento, CA 95817
(916) 734-1537
fax (916) 734-7950
e-mail: jjrichards@ucdavis.edu

Methods: An internet-based survey was designed with questions regarding droperidol use in the emergency department (ED). Data collected included EP demographics, use of droperidol before and after the FDA warning, use of alternative drugs, and incidence of arrhythmias. A representative sample of EPs were contacted by e-mail and asked to complete the survey.

Results: A total of 2,000 e-mails resulted in 506 (25%) completed surveys. There was no second mailing. Responders' average years practicing was 12.6 ± 9.2. EP responders worked in private/community (n=278, 55%), academic/county (n=187, 37%), and HMO (n=41, 8%) hospitals. The majority (n=455, 90%) used droperidol and were aware of the FDA warning (n=460, 91%). Droperidol was no longer available at 122 (24%) of the respondents' EDs as a result of the FDA warning. Prior to the FDA warning, EPs who had used droperidol used it as an antiemetic (n=408, 90%), for control of agitation (n=330, 73%), for treatment of headache (n=247, 54%), and for treatment of vertigo (n=106, 23%). After the FDA warning, 387 (85%) of EPs reported their use of droperidol had decreased or ceased altogether, and 68 (15%) always obtained an electrocardiogram prior to administration. Of those who used droperidol for agitation, 137 (42%) felt there were no other drugs with greater efficacy. Haloperidol was the most cited alternative agent (n=260, 79%) followed by benzodiazepines (n=223, 68%). Of those who used droperidol for antiemesis, 116 (28%) felt there were no other drugs with greater efficacy than droperidol; promethazine was the most cited alternative agent (n=260, 64%). Two (0.4%) EPs reported arrhythmias in patients who received droperidol. Only 37 (8%) EPs reported they were unconcerned with potential loss of droperidol from the market.

Conclusion: Based on this survey, EP use of droperidol has decreased dramatically as a result of the FDA warning. However, EPs believe that there are few or no alternative antiemetic drugs that have an improved adverse effect profile.

Key words: droperidol, Inapsine, emergency medicine, FDA warning

INTRODUCTION:
In December 2001 the FDA issued a "black box warning" (Figure 1), its most serious alert, on the use of droperidol, and this was followed soon thereafter by a similar warning by the Canadian Health Protection Branch.1,2 This warning was in response to concerns over potential prolongation of the QT interval, torsade de pointes, and sudden death after administration of droperidol.3,4 Prior to these warnings, droperidol was extensively used in the ED for myriad indications, including control of agitation and psycho-
Cases of QT prolongation and/or torsades de pointes have been reported in patients receiving INAPSINE at doses at or below recommended doses. Some cases have occurred in patients with no known risk factors for QT prolongation and some cases have been fatal.

Due to its potential for serious proarrhythmic effects and death, INAPSINE should be reserved for use in the treatment of patients who fail to show an acceptable response to other adequate treatments, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs (see Warnings, Adverse Reactions, Contraindications, and Precautions).

Cases of QT prolongation and serious arrhythmias (e.g., torsades de pointes) have been reported in patients treated with INAPSINE. Based on these reports, all patients should undergo a 12-lead ECG prior to administration of INAPSINE to determine if a prolonged QT interval (i.e., QTc greater than 440 msec for males or 450 msec for females) is present. If there is a prolonged QT interval, INAPSINE should NOT be administered.

For patients in whom the potential benefit of INAPSINE treatment is felt to outweigh the risks of potentially serious arrhythmias, ECG monitoring should be performed prior to treatment and continued for 2-3 hours after completing treatment to monitor for arrhythmias.

INAPSINE is contraindicated in patients with known or suspected QT prolongation, including patients with congenital long QT syndrome.

INAPSINE should be administered with extreme caution to patients who may be at risk for development of prolonged QT syndrome (e.g., congestive heart failure, bradycardia, use of a diuretic, cardiac hypertrophy, hypokalemia, hypomagnesemia, or administration of other drugs known to increase the QT interval). Other risk factors may include age over 65 years, alcohol abuse, and use of agents such as benzodiazepines, volatile anesthetics, and IV opiates. Droperidol should be initiated at a low dose and adjusted upward, with caution, as needed to achieve the desired effect.

Figure 1. FDA Black Box Warning for Use of Droperidol (Inapsine®).

METHODS

Study Design and Population

This survey study was specifically designed for, and addressed to practicing EPs in the United States, including those staffing academic/university, county/public, private/community, and health maintenance organization (HMO) EDs. A questionnaire was developed in hyper text markup language (HTML) format using Dreamweaver (Macromedia, San Francisco, California), and a survey world wide web (WWW) page was set up on a dedicated server. Upon completion of the HTML survey, data was collected using ColdFusion (Macromedia, San Francisco, California) in an Access (Microsoft, Redmond, Washington) database for further analysis. This study was approved by the Institutional Review Board of the University of California, Davis Medical Center.

Survey Content and Administration

The first section of the survey contained questions regarding EP demographics, including type of hospital staffed, surrounding population served, and years practicing emergency medicine. We obtained responses on knowledge of the FDA warning and prior use of droperidol in the ED. Current availability of
droperidol in the respondent’s particular ED and discontinuation after the FDA warning were also queried. The next section of the survey involved only those physicians who use or had used droperidol in the ED. Specific indications such as nausea and emesis, agitation, and headache were listed, and frequency of use of droperidol before and after the FDA warning was determined. Emergency physicians who continued to use droperidol despite the FDA warning were asked if they now obtained an electrocardiogram prior to administration. Opinion regarding efficacy of droperidol and preferred alternative pharmaceutical agents for the indications of agitation and psychosis, as well as nausea and emesis, were queried. In addition, adverse outcomes in the form of arrhythmia or sudden death from droperidol administration were tabulated. Finally, EP opinion of the validity of the FDA warning and concern regarding loss of droperidol availability altogether were also included in the questionnaire.

An e-mail containing a solicitation letter detailing the purpose of the study and a hyperlink leading to the study web page was sent to a list of 2,000 EPs. Electronic mail addresses were obtained randomly in proportion to membership number from published directories of the American College of Emergency Physicians, Society of Academic Emergency Medicine, and American Academy of Emergency Medicine. A single broadcast mailing was performed in the Spring of 2002, and there were no repeat e-mails. To ensure privacy and freedom of opinion, no identifiers were used for respondents, such as logging of internet provider (IP) or e-mail addresses, cookies, or survey coding.

### Data Analysis
Comparisons between droperidol use before and after the FDA warning were made using the two-sample Wilcoxon rank sum test for non-parametric variables. Statistical significance is assumed at a level of P < 0.05. Data are reported as mean ± standard deviation.

### RESULTS

From 2,000 e-mails sent out there were 506 (25%) fully completed surveys. There were 122 (6%) invalid e-mail addresses, and one EP returned the e-mail unwilling to participate in the survey. Responders’ average years practicing was 12.6 ± 9.2. Emergency physician responders worked in private/community (n=278, 55%), academic/county (n=187, 37%), and HMO (n=41, 8%) hospitals. One hundred twenty four (25%) described their practice setting as inner city, 299 (59%) as urban, and 83 (16%) as rural. The majority (n=455, 90%) had used droperidol and were aware of the FDA warning (n=460, 91%). Droperidol was no longer available in 122 (24%) of the respondents EDs following the FDA warning. Prior to the FDA warning 90% (n=408) of EPs who had used droperidol, used it as an antiemetic, and 73% (n=330) for control of agitation. Table 1 lists all clinical indications for droperidol as indicated by the respondents.

As a direct result of the FDA warning, 85% (n=387) of EPs reported their use of droperidol had decreased or ceased altogether (Figure 2), and this decline in frequency of use was significant (P < 0.0001). The remaining 15% of EPs who still use droperidol always obtained an electrocardiogram prior to administration. Of those EPs who used droperidol, for the treatment of agitation in the ED, 42% (137) felt there were no other drugs with greater efficacy. Haloperidol was the most frequently cited alternative agent.

| Table 1: Clinical Indications for Droperidol use in the ED. |
|------------|------|-----|
| n          | (%)  |
| EPs who use or used Droperidol | 455  | (100) |

**Indications**

- Emesis: 408 (90)
- Nausea: 380 (84)
- Agitation: 330 (73)
- Psychosis: 265 (58)
- Headache: 247 (54)
- Anxiety: 120 (26)
- Vertigo: 106 (23)
- Abdominal pain: 67 (15)
- Chronic musculoskeletal pain: 59 (13)
- Conscious sedation: 13 (3)
- Amnesia: 8 (2)
- Chest pain: 7 (2)
79% (n=260) followed by benzodiazepines in 68% (n=223) (Table 2). Of those who used droperidol for antiemesis, 28% (n=116) felt there were no other drugs with greater efficacy, and promethazine was the most cited alternative agent by 64% (n=260) (Table 3). Two (0.4%) EPs reported arrhythmias in patients who received droperidol, but no deaths were reported.

Opinion regarding overall utility of droperidol as a drug in the ED declined significantly as a result of the FDA warning (P < 0.001), with 200 (44%) EPs rating droperidol as "extremely useful" prior to the warning, and just 69 (15%) giving it the same rating after the warning. Three hundred and four respondents (67%) answered that the FDA warning had a direct affect on their ability to treat patients in the ED. Emergency physicians were queried on their opinion of the FDA warning, and 242 (53%) felt it was unjustified. Twenty (4%) EPs felt the warning was completely appropriate, and two (0.4%) felt droperidol should be banned altogether. Only 37 (8%) EPs reported they were unconcerned with potential loss of droperidol from the market, as has occurred in Europe.

DISCUSSION

The results of this survey demonstrate the impact the FDA warning on droperidol has had on practicing EPs' use of the drug. Those participating in the survey now use droperidol much less frequently or not at all, and many now have no access to droperidol. It also outlines the skepticism many EPs harbor toward the validity and appropriateness of the FDA warning, and that alternative medications may not be perceived to be as effective as droperidol for a variety of indications. The actual practice experience of EPs does

**Table 2.** Equal or More Effective Alternative Drugs than Droperidol for Agitation in the ED.

| Alternative agents                          | n  | (%) |
|--------------------------------------------|----|-----|
| Haloperidol (Haldol®)                      | 260| (79)|
| Benzodiazepines                            | 223| (68)|
| Chlorpromazine (Thorazine®)                | 22 | (7 )|
| Barbiturates                               | 17 | (5 )|
| Propofol (Diprivan®)                       | 14 | (4 )|
| Risperidone (Risperdal®)                   | 4  | (1 )|
| Olanzapine (Zyprexa®)                      | 2  | (0.6)|
| Thioridazine (Mellaril®)                   | 2  | (0.6)|
| Fluphenazine (Prolixin®)                   | 2  | (0.6)|
| Diphenhydramine (Benadryl®)                | 1  | (0.3)|

**Figure 2.** Frequency of Droperidol Use before and after the FDA Warning.
Table 3. Equal or More Effective Alternative Drugs than Droperidol for Nausea and Emesis in the ED.

| Drug                          | EPs (%) |
|-------------------------------|---------|
| Promethazine (Phenergan®)     | 260 (64) |
| Metoclopramide (Reglan®)     | 201 (49) |
| Ondansetron (Zofran®)         | 187 (46) |
| Prochlorperazine (Compazine®) | 123 (30) |
| Hydroxyzine (Vistaril®)       | 95 (23)  |
| Diphenhydramine (Benadryl®)  | 57 (14)  |
| Meclizine (Antivert®)         | 48 (12)  |
| Trimethobenzamide (Tigan®)   | 30 (7)   |
| Dolasetron (Anzemet®)        | 8 (2)    |
| Lorazepam (Ativan®)          | 5 (1)    |
| Scopolamine (Transderm Scop®)| 4 (1)    |
| Granisetron (Kytril®)        | 4 (1)    |
| Dexamethasone (Decadron®)    | 1 (0.2)  |
| Ginger root                  | 1 (0.2)  |

not seem to reflect the potential for adverse outcome as stated by the FDA. What is unique about droperidol is it is one of the few drugs used for a wide range of seemingly unrelated clinical indications, as reflected in recent emergency medicine literature.\textsuperscript{6,7,10,19-24} Its efficacy and extremely low cost may also explain the outcry that accompanied its loss in Europe. After the complete withdrawal of droperidol in Europe by its manufacturer Janssen-Cilag, Tramer and colleagues emphasized the discontinuation was in response to adverse events linked with chronic, large oral doses given to psychiatric patients, not the smaller intravenous doses given to PONV patients.\textsuperscript{30} This group called for a distinction to be made between the two indications so that low-dose intravenous droperidol could be used in the perioperative setting. Haines et al also emphasized this distinction, and mentioned the consequences to the national health budget in the United Kingdom from loss of droperidol and use of the newer serotonin type 3 antagonists.\textsuperscript{31} A similar protest was heard from Lehot and Ferry in France.\textsuperscript{32}

Following the FDA warning, an even stronger outcry occurred in the United States. In an article investigating the actual adverse outcomes listed by the FDA, Horowitz and associates, referring to droperidol as “one of the most used emergency medications now,” suggested the link between droperidol and QT interval prolongation, torsade de pointes, and sudden cardiac death was not at all clear.\textsuperscript{4} They noted many of the deaths or adverse outcomes provided by the FDA were patients who were already critically ill and/or concomitantly taking several potentially arrhythmogenic medications. Bailey et al similarly investigated the actual adverse cases used by the FDA to justify the warning and reached the same conclusion.\textsuperscript{33} Gan and colleagues determined the cost of preventing PONV was over 40 times higher to the patient when ondansetron was used instead of droperidol, and that prior to the FDA warning droperidol had a 30% market share.\textsuperscript{29} This group wrote “we believe that the recent black box warning by the FDA is totally unjustified,” and called for the FDA to lift the ban for low-dose droperidol.

Kantor emphasized the serotonin type 3 antagonists, such as ondansetron and dolasetron, also had potential for QT interval prolongation and torsade de pointes that was largely being ignored by the FDA.\textsuperscript{36} An updated list of drugs that prolong the QT interval or induce torsade de pointes may by found on the internet (www.torsades.org), and include chlorpromazine, dolasetron, haloperidol, risperidone, thiopridazine, and ziprasidone, all drugs listed by survey respondents as potential alternatives to droperidol (Tables 2 and 3). Many EPs and anesthesiologists are concerned that the restriction of droperidol and limited availability of prochlorperazine is forcing them to use of more expensive serotonin type 3 antagonists such as ondansetron.\textsuperscript{37} These drugs do not have a record of extensive use, may have similar adverse effects, and are extremely expensive.

LIMITATIONS

The most important limitation of this study is that it is a survey based on subjective answers and opinions of a small sample of EPs, and may not reflect actual practice. Furthermore, those who responded may have been motivated to do so because of a stronger than average positive or negative opinion regarding droperidol. There were many non-responders, and several inaccurate, invalid, or expired e-mail addresses. The loss of these potential survey partici-
pants may have affected the results of the study. In order to maintain respondents' privacy, follow up sur-
veys were not e-mailed to non-responders, or to those submitting incomplete surveys. Respondents may have felt their participation in the survey would result in their e-mail identity being promulgated.

CONCLUSION
Among those EPs replying to this survey, use of droperidol decreased dramatically as a result of the
FDA warning. Over half the survey respondents feel the FDA warning is unjustified and are concerned by
the potential loss or further restriction of droperidol in the United States. Many of the drugs listed by EPs as
alternatives to droperidol, such as haloperidol, chlor-
promazine, risperidone, and dolasetron also have risk
of QT interval prolongation. Because of limited alter-
native therapies, as well as their side effect profile
and expense, many EPs and anesthesiologists ques-
tion the FDA's action.

REFERENCES
1. U.S. Food and Drug Administration. FDA strengthens
warnings for droperidol. FDA Talk Paper 2001;T01-62.
2. Wooltorton E. Droperidol: cardiovascular toxicity and
deaths. CMAJ 2002;166:932.
3. Glassman AH, Bigger JT Jr. Antipsychotic drugs:
prolonged QTc interval, torsade de points, and sudden
death. Am J Psychiatry 2001;158:1774-82.
4. Horowitz BZ, Bizovi K, Moreno R. Droperidol – behind
the black box warning. Acad Emerg Med 2002;9:615-618.
5. Cure S, Carpenter S. Droperidol for acute psychosis.
Cochrane Database Syst Rev 2001;(2):CD002830.
6. Richards JR, Derlet RW, Duncan DR. Chemical restraint
for the agitated patient in the emergency department:
lorazepam versus droperidol. J Emerg Med. 1998;16:567-73.
7. Thomas H Jr, Schwartz E, Petrilli R. Droperidol versus
haloperidol for chemical restraint of agitated and combative
patients. Ann Emerg Med 1992;21:407-13.
8. Chambers RA, Druss BG. Droperidol: efficacy and side
effects in psychiatric emergencies. J Clin Psychiatry
1999;60:664-7.
9. Brown ES, Dilsaver SC, Bowers TC, Swann AC.
Droperidol in the interim management of severe mania: case
reports and literature review. Clin Neuropharmacol
1998;21:316-8.
10. Hick JL, Mahoney BD, Lappe M. Prehospital sedation
with intramuscular droperidol: a one-year pilot. Prehosp
Emerg Care 2001;5:391-4.
11. Hameer O, Collin K, Ensom MH, Lomax S. Evaluation of
droperidol in the acutely agitated child or adolescent. Can
J Psychiatry 2001;46:864-5.
12. Stanislav SW, Childs A. Evaluating the usage of
droperidol in acutely agitated persons with brain injury.
Brain Inj 2000;14:261-5.
13. Eberhart LH, Morin AM, Bothner U, Georgieff M.
Droperidol and 5-HT3-receptor antagonists, alone or in
combination, for prophylaxis of postoperative nausea and vomit-
ing. A meta-analysis of randomised controlled trials. Acta
Anaesthesiol Scand 2000;44:1252-7.
14. Macario A, Chung A, Weinger MB. Variation in prac-
tice patterns of anesthesiologists in California for prophy-
laxis of postoperative nausea and vomiting. J Clin Anesth
2001;13:353-60.
15. Rizzo J, Bernstein D, Gress F. A randomized double-
blind placebo-controlled trial evaluating the cost-effective-
ness of droperidol as a sedative premedication for EUS.
Gastrointest Endosc 1999;50:178-82.
16. Hill RP, Lubarsky DA, Phillips-Bute B, Fortney JT, Creed
MR, Glass PSA, Gan TJ. Cost-effectiveness of prophylactic
antiemetic therapy with ondansetron, droperidol, or placebo.
Anesthesiology 2000;92:958-67.
17. Lim BS, Pavy TJ, Lumsden G. The antiemetic and dys-
phoric effects of droperidol in the day surgery patient.
Anaesth Intens Care 1999;27:371-4.
18. Kreisler NS, Spiekermann BF, Ascari CM, Rhyne HA,
Kloth RL, Sullivan LM, Durieux ME. Small-dose droperidol
effectively reduces nausea in a general surgical adult pa-
tient population. Anesth Analg 2000;91:1256-61.
19. Vinson DR. Treatment patterns of isolated benign head-
ache in US emergency departments. Ann Emerg Med
2002;39:215-22.
20. Miner JR, Fish SJ, Smith SW, Biros MH. Droperidol vs.
prochlorperazine for benign headaches in the emergency
department. Acad Emerg Med 2001;8:873-9.
21. Richman PB, Allegra J, Eskin B, Doran J, Reischel U,
Kaiatlas C, Nashed AH. A randomized clinical trial to assess
the efficacy of intramuscular droperidol for the treatment of
acute migraine headache. Am J Emerg Med. 2002;20:39-42.
22. Baldwin RL. Droperidol in the treatment of vertigo.
South Med J. 1983;76:1271-2.
23. Johnson WH, Fenton RS, Evans A. Effects of droperidol
in management of vestibular disorders. Laryngoscope.
1976;86:946-54.
24. Irving C, Richman PB, Kaiafas C, Eskin B, Ritter A, Allegra J. Droperidol for the treatment of acute peripheral vertigo. Am J Emerg Med. 1999;17:109-10.

25. Graf J, Janssens U. Therapy of angina pectoris: morphine or thalamonal? Dtsch Med Wochenschr 2001;126:572-3.

26. Burduk P, Guzik P, Piechocka M, Bronisz M, Rozek A, Jadon M, Jordan MR. Comparison of fentanyl and droperidol mixture (neuroleptanalgesia II) with morphine on clinical outcomes in unstable angina patients. Cardiovasc Drugs Ther 2000;14:259-69.

27. Wajima Z, Shitara T, Inoue T, Ogawa R. Severe lightning pain after subarachnoid block in a patient with neuropathic pain of central origin: which drug is best to treat the pain? Clin J Pain 2000;16:265-9.

28. Kotake Y, Matsumoto M, Ai K, Morisaki H, Takeda J. Additional droperidol, not butorphanol, augments epidural fentanyl analgesia following anorectal surgery. J Clin Anesth. 2000;12:9-13.

29. Gan TJ, White PF, Scuderi PE, Watcha MF, Kovac A. FDA “Black Box” warning regarding use of droperidol for postoperative nausea and vomiting: Is it justified? Anesthesiology 2002;97:287.

30. Tramer MR, Reynolds DJ, Goodman NW. Whose drug is it anyway? Lancet 2001;358:1275.

31. Haines J, Barclay P, Wauchob T. Withdrawal of droperidol (droperidol). BMJ 2001;322:1603.

32. Lehot JJ, Ferry S. And now we present droperidol! Anesth Intensiv Ther 2001;20:499-500.

33. Bailey P, Norton R, Karan S. The FDA droperidol warning: is it justified? Anesthesiology 2002;97:288-289.

34. Ben-David B, Weber S, Chernus S. Droperidol “black box” warning warrants scrutiny. Anesthesiology 2002;97:288.

35. Young D. Black box warning for droperidol surprises pharmacists. Am J Health Syst Pharm 2002;59:502-504.

36. Kantor GS. Arrhythmia risk of antiemetic agents. Anesthesiology 2002;97:286.

37. Lenzer J, Solomon RC. The droperidol dilemma. ACEP News 2002;August.

Resident/Student Corner

Training in emergency medicine is full of fascinating encounters. Over the course of medical school and residency we will amass a huge body of intangible experience. Much of this we share with our immediate peers, residents, and classmates, as a part of our own coping and cataloguing mechanisms. However, much of it is also an important part of our learning process. I cannot begin to relay how much I have learned, not from books (I will never read as much as my residency director would like me to) but from the experience of my fellow residents. Not only have I learned about the practice of medicine, but about the practice of life as a medical professional.

This is a new section for this journal. As it stands there are no official boundaries. We (the collective resident/student population) can fill it as we see fit. There are many outlets for statistically significant randomized, blinded, meta-prospective studies about variable dosing of phenytoin in post-ictal rats. However, there are very few places to share on a wider front, the more nebulous, but not necessarily less important experiential aspects of our training. (Wow, that sounds a bit ‘new-age.’) Hopefully this will spark some interesting discussion and we can learn and laugh a little in the process.

Submissions of any kind (interesting stories, poems, prose, fact, fiction, and outside-the-box research proposals) may be sent to Jason Quinn jquinn@hghed.com.