

ORIGINAL RESEARCH

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

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ABSTRACT:

Objectives: To determine if emergency physicians' (EP) use of droperidol has changed since the United States Food and Drug Administration (FDA) warning of December 2001 concerning QT interval prolongation, torsade de pointes, and sudden death; and to query EP opinions regarding droperidol before and after the FDA warning and regarding potential alternative drugs.

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-

WARNING

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®).

sis,⁵⁻¹² nausea and emesis,¹³⁻¹⁸ headache,¹⁹⁻²¹ vertigo,²²⁻²⁴ and atypical pain syndromes.²⁵⁻²⁸ Droperidol was commonly used by anesthesiologists for treatment of postoperative nausea and vomiting (PONV), constituting 30% of the PONV market, with over 25 million units sold in 2000.²⁹ In its oral form, droperidol was used as an antipsychotic agent by psychiatrists, especially in Europe.³ Before the FDA warning, only doses greater than 25 mg were considered to be at risk for QT interval prolongation and arrhythmia. Across the world, EPs, anesthesiologists, psychiatrists, and pharmacists reacted with skepticism to these new restrictions on the use of droperidol.^{4,29-35} The purpose of this survey study was to determine if droperidol use by EPs has changed since the FDA warning.

METHODS

Study Design and Population

This survey study was specifically designed for, and addressed to practicing EPs in the United States, in-

cluding 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 \pm standard deviation.

RESULTS

Table 1. Clinical Indications for Droperidol use in the ED.

	<u>n</u>	<u>(%)</u>
EPs who use or used Droperidol	455	(100)
<i>Indications</i>		
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)

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

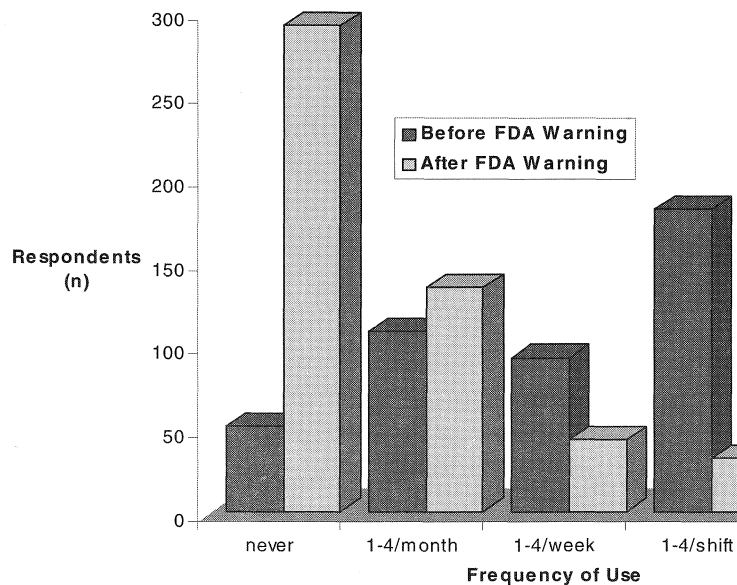


Figure 2. Frequency of Droperidol Use before and after the FDA Warning.

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.

	n	(%)
EPs who use or used droperidol for agitation	330	(100)
<i>Alternative agents</i>		
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)

Table 3. Equal or More Effective Alternative Drugs than Droperidol for Nausea and Emesis in the ED.

	n	(%)
EPs who use or used droperidol for antiemesis	408	(100)
<i>Alternative agents</i>		
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.^{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.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.³¹ A similar protest was heard from Lehot and Ferry in France.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.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.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.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 FDA³⁶. An updated list of drugs that prolong the QT interval or induce torsade de pointes may be found on the internet (www.torsades.org), and include chlorpromazine, dolasetron, haloperidol, risperidone, thioridazine, 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.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 surveys 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, chlorpromazine, risperidone, and dolasetron also have risk of QT interval prolongation. Because of limited alternative therapies, as well as their side effect profile and expense, many EPs and anesthesiologists question the FDA's action.

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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-agey.') 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@ghed.com.