Droperidol—Behind the Black Box Warning

On December 4, 2001, the Food and Drug Administration (FDA) sent an advisory that it was adding an important drug warning to droperidol. In a ''Dear Health Care Professional'' letter from the company, they warned, in bold type, that there were ''**reports of deaths associated with QT prolongation and torsade de pointes in patients treated with doses of inapsine (Droperidol) above, within and even below the approved range**.''

Where did these death reports come from? What was the scientific rationale to recommend that droperidol not be given for a QTc greater than 440 msec for males and 450 msec for females? Why was perhaps one of the most used emergency medications now, as the revised package insert currently states, ''reserved for use in the treatment of patients who fail to show an acceptable response to other adequate treatments''? And what really are these other treatment options?

In an effort to understand the reasons behind these warnings, we wrote to Akorn Pharmaceuticals, the sole U.S. manufacturer of droperidol, marketed as Inapsine, for an explanation. The reply provided the following information: ''The FDA required labeling changes for droperidol after it received reports of 100 unique spontaneous cardiovascular adverse events following droperidol administration, 20 of which involved torsade de pointes or prolongation of the QT interval. Eighteen of the cases resulted in death, six of which were attributed to torsade or QT prolongation. Five deaths occurred at or below the labeled doses of 2.5 mg.''

Next stop—the FDA. Under the Freedom of Information Act, we acquired the printout of spontaneous reports submitted to the FDA. These 271 reports occurred between November 1997 and December 2001. After a review of these records, it appeared that some of these cases represented the same patients reported by different sources. Cases that matched by age, gender, and medication list were eliminated as duplicate and triplicate reports. This left us with what appeared to be 93 unique instances of death reported in association with droperidol use. Interestingly, many of these deaths were reported by foreign sources, which should not lessen the importance of their occurrence. However, in Europe, droperidol comes as Droleptan, and is packaged for parenteral use at twice the concentration as Inapsine. Fifty-two deaths occurred after use of droperidol in doses above 10 mg, many in the 50- to 100-mg intramuscular (IM) range. An additional 22 cases did not list the dose, but many of these were also non-U.S. reports. A second drug, dehydrobenzperidol, the oral equivalent of droperidol, was also reported in a few cases, some in patients taking it on a chronic basis, and daily doses ranging as high as 250 mg.

On March 31, 2001, Janssen-Cilag Ltd., the manufacturer of Droleptan, discontinued both the parenteral and oral formulations of the drug after the Medicines Control Agency, the United Kingdom's equivalent of the FDA, raised concerns about QT prolongation, and the company did their own risk–benefit assessment. Physicians of patients receiving the oral drug were advised to taper it, and find an alternative therapy.

Surprisingly within the FDA report, 71 of the total cases, including 55 of the deaths, were reported on July 9, 2001, possibly by a single source. On this single day, nine out of a total of 11 cases of torsade and four out of a total of seven cases of QT prolongation were reported. In the only two other cases of torsade, droperidol was believed to be a ''secondary suspect'' drug. Antivert was thought to be the primary medication responsible in the first case, and a list of 16 other medications, including cyclobenzaprine delineated as the primary suspect medication, were included in the second case. Both of these cases were reported more than once, slightly inflating the total number of torsade or long QT to 20; there were actually only 18 cases attributed to either torsade or QT prolongation. Of the July 9, 2001, case series, the five deaths, out of the nine torsade cases, were due to a greater than ''200 ml flush.'' Only one death was associated with a low-dose case. This case involved a 52-year-old male, whose other listed medications included vasopressin and nitroglycerin, who received of 3.75 mg of droperidol. His comorbid diagnosis included pulmonary edema and ''low hemoglobin.'' One is left to conjecture what may have been the cause of death. Of the July 9, 2001, long QT cases, none resulted in death. One patient was given 0.25 mg/kg of droperidol resulting in QT prolongation and cardiac arrest, but this case was not listed as a death. This large intravenous (IV) dose is common in the European literature, where a clear dose-response curve of high-dose droperidol has been shown to lengthen the QT interval.[1]

What about those doses ''below the approved range,'' the ones we usually give for agitation, headaches, nausea, vomiting, and sedation in the practice of emergency medicine? There were 13 cases of deaths, with doses less than 10 mg, out of the total 93 deaths. One case involved someone tak-

ing droperidol orally 5 mg QID along with clozapine 450 mg/day. Two others were with repeat doses of droperidol, one of which also listed dopamine, dobutamine, epinephrine drips, and several other medications. This leaves ten cases in which standard U.S. doses were used and death occurred. Three were clearly anesthetic-related cases with inhalational agents, fentanyl derivatives, and neuromuscular-blocking agents on these medication lists. None of these cases were coded as torsade or long QT, leaving one to wonder what the cause of death was. However, one case was with a dose of 0.625 mg, and another case was with 0.25 mg orally in which the patient died in atrioventricular block. These doses are practically in the homeopathic range, and more detailed accounting of these cases would need to be scrutinized to implicate droperidol. The remaining five cases were with 5 mg of droperidol, one of these given with 50 mg of diphenhydramine. So with this small handful of suspect cases the wheat is separated from the chaff on the number of deaths from droperidol. A lone handful of cases of low-dose droperidol is what we are left with, although we suspect that there could be more, as the voluntary Medwatch system underrepresents the adverse drug effects that occur in practice. It is based upon these few cases that one is forced now to make the decision—whither droperidol?

But are there safer substitutions we can use, or at least try to see whether there is an ''acceptable response to other adequate treatments'' hinted at by the black box warning? For nausea and vomiting there are other choices: metoclopramide (Reglan), promethazine (Phenergan), prochlorperazine (Compazine), and odansetron (Zofran). Unfortunately, the emergency medicine literature on nausea/vomiting management is quite thin. Most of our knowledge comes from the anesthesia and oncology literature.

Metoclopramide is often thought of more as a prokinetic agent than as an antiemetic and has been used in the emergency department (ED) in small doses (10 mg IV) to prevent emesis of radiographic contrast.[2] Although higher doses of metoclopramide (from 20–40 mg IV to 2 mg/kg) may be effective in patients receiving N-acetylcysteine (NAC)[3] and in chemotherapy patients,[4] high-dose regimens have not been studied in the undifferentiated ED patient population and are not commonly used in the ED. Promethazine (Phenergan) has been approved by the FDA since 1955 and is generally thought to be a reasonably effective antiemetic, with sedation and dystonia being among its side effects. Despite its widespread use, there is surprisingly little literature for its use as an antiemetic.

In one of the few double-blinded ED studies, compazine was shown to be superior to phenergan in controlling nausea/vomiting.[5] Prochlorperazine (Compazine) does have side effects, however, including a significant rate of akathisia in some series,[6,7] which can be reduced by coadministration of diphenhydramine.[8] This may all be a moot point, however, as the manufacturers of Compazine are no longer releasing the drug.

This leaves us with the 5-HT_3 receptor antagonists, of which ondansetron (Zofran) is an example. Again, there is no high-quality placebo-controlled ED-based literature to guide us, so looking at studies involving the treatment of established postoperative nausea and vomiting (PONV) may give us our best advice. A recent published review of this literature finds a 20–30% absolute reduction in nausea and vomiting when compared with placebo.[9] However, many of the large anesthesia-based studies looking at the 5-HT_3 antagonists look at prevention and not treatment of nausea and vomiting. The 5-HT_3 antagonists have earned a first-line recommendation for the treatment of established PONV by the American Society of Health-System Pharmacists,[10] ironically alongside droperidol. One abstract in the emergency medicine literature suggests, however, that ondansetron may be effective for acute gastroenteritis in pediatric patients, without causing the side effects shared by all the other phenothiazines agents.[11]

Should the 5-HT_3 antagonists be a first-line agent in the ED for treating nausea and vomiting? They certainly have a favorable safety profile, with headache being the major side effect. The toxicology literature has a handful of case reports suggesting that ondansetron can be an effective rescue antiemetic.[12–14] Given the currently available alternatives, the 5-HT_3 antagonists seem like a viable alternative. Their major drawback is cost. Ondansetron, which is not scheduled to come off patent until 2005, costs approximately $26 per 4-mg IV dose, while droperidol costs $0.88 for a 2.5-mg ampule, and promethazine (Phenergan) costs $3 for a 50-mg ampule.

For the patient with severe agitation there is parenteral haloperidol, another butyrophenone. Haloperidol has been shown to causes QT prolongation and torsade.[15,16] Droperidol has been demonstrated to have more rapid onset and greater efficacy than haloperidol alone for patients with acute psychosis,[17] and undifferentiated agitated behavior in the ED.[18] Haloperidol and lorazepam in combination are more effective and rapid than haloperidol alone, but there is no direct comparison with droperidol.[19] Other atypical antipsychotic medications, although unavailable parenterally at this time, in-

cluding clozapine, risperidone, olanzapine, quetiapine, and sertindole, have all been shown to lengthen the QT interval.[20–22] Benzodiazepines have been used for the agitated delirium associated with amphetamine toxicity, clearly one of the most high-risk cardiovascular scenarios, but were found less effective than droperidol, and required more repeat dosing in one center.[23] Additionally the need to administer these agents intramuscularly in the severely agitated patient leads to unpredictable rates of absorption for many of these agents, but not droperidol.

Droperidol has substantial benefit in the acutely agitated patient when time is critical, but we should acknowledge the risk as well and minimize its use. The use of either droperidol or haloperidol should be reserved for those patients who are an immediate risk to themselves or others. In less dangerous situations, alternatives include IM benzodiazepines, oral benzodiazepines, or other antipsychotic medications and comfort measures such as food or a quiet place to sit or lie down.

Finally, what should the hundreds of emergency physicians, who undoubtedly have used millions of doses of droperidol safely and without side effects in the last decade, do as a result of this warning? In an audit in five major hospitals in our metropolitan area, more than 38,000 doses of droperidol are dispensed annually, with 1,200 of those being used in our ED. Clearly, higher doses of droperidol, as used in Europe, prolong the QT interval. Can low doses be safely used prior to obtaining an electrocardiogram (ECG)? Does a baseline ECG, with a QT in excess of the guidelines laid out in the black box warning, truly indicate patients at risk? Prospective research will be needed to address these issues and to prove that droperidol is a safe and effect drug for these indications. A recent prospective randomized study comparing droperidol with meperidine has shown equal efficacy and safety of droperidol in acute migraine.[24] A prospective randomized pilot study involving 40 patients with acute vertigo in this issue of *Academic Emergency Medicine* shows that both droperidol and dimenhydrinate allowed less than 50% of each group to be discharged from the ED with reduction in symptoms.[25]

Despite the new warning, we should take it as just that, a *warning* to think a little more before we use droperidol. Droperidol will certainly continue to have a role in the emergency medicine armamentarium. Perhaps our use of droperidol for the many symptoms for which patients present to an ED has come home to roost. It may be that we need a mid-course correction on a drug that, like the dot.coms, soared to high levels. We need to reevaluate our use of a drug that suffered from the emergency medicine equivalent of ''irrational exuberance.''—**B. Zane Horowitz, MD** (horowiza@ohsu.edu), **Kenneth Bizovi, MD**, and **Raymond Moreno, MD,** *Oregon Health & Science University, Portland, OR*

References

1. Lische V, Behne M, Doelken P, Schledt U, Probst S, Vettermann J. Droperidol causes a dose-dependent prolongation of the QT Interval, Anesth Analg. 1994; 79:983–6.
2. Page B, Dallara J. Metoclopramide in trauma CT scanning: preventing emesis of oral radiographic contrast. Am J Emerg Med. 1996; 14:373–6.
3. Wright RO, Anderson AC, Lesko SL, Woolf AD, Linakis JG, Lewander WJ. Effect of metoclopramide dose on preventing emesis after oral administration of N-acetylcysteine for acetaminophen overdose. J Toxicol Clin Toxicol. 1999; 37:35–42.
4. Olver IN, Wolf M, Laidlaw C, et al. A randomized double-blind study of high-dose intravenous prochlorperazine versus high-dose metoclopramide as antiemetics for cancer chemotherapy. Eur J Cancer. 1992; 28A:1798–802.
5. Ernst AA, Weiss SJ, Park S, Takakuwa KM, Diercks DB. Prochlorperazine versus promethazine for uncomplicated nausea and vomiting in the emergency department: a randomized, double-blind clinical trial. Ann Emerg Med. 2000; 36:89–94.
6. Drotts DL, Vinson DR. Prochlorperazine induces akathisia in emergency patients. Ann Emerg Med. 1999; 34: 469–75.
7. Olsen JC, Keng JA, Clark JA. Frequency of adverse reactions to prochlorperazine in the ED. Am J Emerg Med. 2000; 18:609–11.
8. Vinson DR, Drotts DL. Diphenhydramine for the prevention of akathisia induced by prochlorperazine: a randomized, controlled trial. Ann Emerg Med. 2001; 37:125–31.
9. Kazemi-Kjellberg F, Henzi I, Tramer MR. Treatment of established postoperative nausea and vomiting: a quantitative systematic review. BMC Anesthesiol. 2001; 1:2.
10. ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery. Am J Health Syst Pharm. 1999; 56:729–64.
11. Ramsook C, Sahagun-Carreon I, Kozinetz CA, Moro-Sutherland DM. A randomied clinical trial comparing oral ondansetron with placebo in children with vomiting from acute gastroenteritis. Ann Emerg Med. 2002; 39: 397–403.
12. Roberts JR, Carney S, Boyle SM, Lee DC. Ondansetron quells drug-resistant emesis in theophylline poisoning. Am J Emerg Med. 1993; 11:609–10.
13. Tobias JD, Gregory DF, Deshpande JK. Ondansetron to prevent emesis following N-acetylcysteine for acetaminophen intoxication. Pediatr Emerg Care. 1992; 8:345–6.
14. Clark RF, Chen R, Williams SR, Johnson CL, Harchelroad F. The use of ondansetron in the treatment of nausea and vomiting associated with acetaminophen poisoning. J Toxicol Clin Toxicol. 1996; 34:163–7.
15. Jackson T, Ditmanson L, Brendan P, Torsade de pointes and low dose oral haloperidol. Arch Intern Med. 1997; 157:2013–5.
16. Sharma ND, Rosman HS, Padhi D, Tisdale JE. Torsade de pointes associated with Intravenous haloperidol in critically ill patients. Am J Cardiol. 1998; 81:238–44.
17. Resnick M, Burton BT. Droperidol versus haloperidol in the initial management of agitated patients. J Clin Psychiatry. 1984; 45:298–9.

18. Thomas H, Schwartz E, Petrilli R. Droperidol versus haloperidol for chemical restraint of agitated and combative patients. Ann Emerg Med. 1992; 21:407–13.
19. Battaglia J, Moss S, Rush J, et al. Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. Am J Emerg Med. 1997; 15:335–40.
20. Burns MJ, The pharmacology and toxicology of atypical antipsychotic agents. J Toxicol Clin Toxicol. 2001; 39:1–14.
21. Lawrence KR, Nasraway SA. Conduction disturbances associated with administration of butyrophenone antipsychotics in the critically ill: a review of the literature. Pharmacotherapy. 1997; 17:531–7.
22. Glassman AH, Bigger JT. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. Am J Psychiatry. 2001; 158:1774–82.
23. Richards JR, Derlet RW, Duncan DR. Methamphetamine toxicity: treatment with a benzodiazepine versus a butyrophenone. Eur J Emerg Med. 1997; 4:130–5.
24. Richman PB, Allegra J, Eskin B, et al. A randomized clinical trail to assess the efficacy of intramuscular droperidol for the treatment of acute migraine headache. Am J Emerg Med. 2002; 20:39–42.
25. Irving C, Richman P, Kaiafas C, Eskin B, Allegra J. Intramuscular droperidol versus intramuscular dimenhydrinate for the treatment of acute peripheral vertigo in the emergency department: a randomized clinical trial. Acad Emerg Med. 2002; 9:650–3.