# CORRESPONDENCE

## The Use and Safety of Droperidol in a High-risk, Inner-city Emergency Department Patient Population

*To the Editor:*—We commend Drs. Chase and Biros on the review of their experience with the use of droperidol in their medical center. Their hypothesis was that ''droperidol would be safe and effective in all patients.''[1] Their definition of adverse effects failed to include, however, the most concerning adverse effect of the use of droperidol and the reason that the black box warning was issued: QT prolongation and malignant cardiac arrhythmias—torsades de pointes.

The Food and Drug Administration (FDA) placed a now-familiar black box warning on droperidol in December 2001 because of its propensity to prolong the QT interval and associated case reports of torsades de pointes.[2,3] Further review of the literature confirms that droperidol has been shown to lengthen the QT interval in a dose-dependent fashion, and its mechanism has been described.[4–6] Drs. Chase and Biros report that most patients did not receive serial electrocardiograms (ECGs), and most patients given droperidol were not on continuous cardiac monitors in their emergency departments (EDs) during the droperidol observation period. Torsades de pointes is a dysrhythmia that typically spontaneously terminates, and it may not be noted unless syncope occurs, or it is captured by a continuous cardiac monitor. The authors were not able to comment on this serious and potentially life-threatening complication of droperidol.

The authors' report of the indications for the use of droperidol was primarily for agitation (82% of cases) from multiple causes, many of which were documented alcohol intoxication, and/or trauma; some trauma patients had sustained head injuries. The choice of a neuroleptic (butyrophenone) medication in this patient population as a primary therapy should be cautioned because there is an increased risk of seizures and it may worsen alcohol withdrawal.[7,8] Drs. Chase and Biros acknowledge these risks, and although they did not observe any increased incidence of seizures in their study, the availability of efficacious medications with better safety profiles (i.e., benzodiazepines) should not be disregarded. We contend that other classes of medications should be used as primary therapy for the indications listed in their study.

Although Drs. Chase and Biros' retrospective study is well designed to prove their hypothesis that the routine use of droperidol seems to be safe in ''high-risk'' ED patients, they do not have the power to prove its safety. The use of droperidol on every agitated patient would be a dangerous practice, and the risk-to-benefit ratio always should be measured before administering any medication.—**Sean Keenan, MD**, **Fernando Orellana, MD,** and **Fermin Barrueto Jr., MD** (fbarrueto@hotmail.com), *New York City Poison Control Center, New York, NY*

### References

1. Chase PB, Biros MH. A retrospective review of the use and safety of droperidol in a large, high-risk, inner-city emergency department patient population. Acad Emerg Med. 2002; 9: 1402–10.
2. http://www.fda.gov/bbs/topics/ANSWERS/2001/ANS01123.html.
3. Michalets EL, Smith LK, Van Tassel ED. Torsades de pointes resulting from the addition of droperidol to an existing cytochromes P450 drug interaction. Ann Pharmacother. 1998; 32(7–8):761–5.
4. Drolet B, Zhang S, Deschenes D, et al. Droperidol lengthens cardiac repolarization due to block of the rapid component of the delayed rectifier potassium current. J Cardiovasc Electrophysiol. 1999; 10:1597–604.
5. Reilly JG, Ayis SA, Ferrier IN, et al. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. Lancet. 2000; 355:1048–52.
6. Lischke V, Behne M, Doelken P, et al. Droperidol causes a dose-dependent prolongation of the QT interval. Anesth Analg. 1994; 79:983–6.
7. Herrick IA, Craen RA, Belb AW, et al. Propofol sedation during awake craniotomy for seizures: patient-controlled administration versus neuroleptic analgesia. Anesth Analg. 1997; 84:1285–91.
8. Mayo-Smith MF, for the American Society of Addictive Medicine Working Group. Pharmacological management of alcohol withdrawal. JAMA. 1997; 278:144–51.

•

*In reply:*—We thank Drs. Keenan, Orellana, and Barrueto for their thoughtful letter regarding our retrospective review of the use and safety of droperidol (Inapsine) and for reminding us of the FDA's concerns about its use. We appreciate these comments and concerns, but we need to reaffirm our purpose, our conclusion, and the limitations of our study. It was not our intent to minimize the FDA's black box warning regarding this drug or the adverse events that can occur after its use.

We began using droperidol in our ED several years ago as an alternative to haloperidol, when faced with extremely agitated patients at risk of self-injury or uncooperative with emergent, necessary medical management. Many of these patients were alcohol and/or cocaine intoxicated, were experiencing an agitated postictal state, or were agitated head-injured patients. Droperidol provided smooth rapid sedation, which, in our opinion, resulted in fewer dystonic reactions and a shorter duration of sedation than haloperidol. These difficult patients had more rapid medical management and a shorter ED length of stay than we had observed with patients receiving haloperidol. We began to use droperidol

almost exclusively in this agitated patient population and for treatment of nausea and various pain syndromes.

We have always appreciated droperidol's potential for adverse events. We performed a retrospective review of patients receiving droperidol in our ED in 1998, before the FDA's black box warning. We wanted to see if we were putting these patients, many of whom were already at risk for seizures, at even higher risk, by giving them a drug that is thought to lower the seizure threshold.[1,2] We also screened for other potential adverse events after patients received droperidol, including any detected "serious complications" (i.e., respiratory depression, cardiac arrest) and "minor adverse events," such as the occurrence of dystonic reactions, akathisia, and easily reversible hypotension. We found that only a few ($n = 5$) of these "high-risk" patients ($n = 883$) had seizures after droperidol, and all had significant comorbidities that could have contributed to or caused the seizure (cocaine in two patients; hypoxia, one patient; alcohol withdrawal, one patient; meningitis, one patient). Other minor adverse events also were seen, but infrequently. Although most patients were not on cardiac monitors and did not have ECGs performed during the course of their care, they were observed continuously in the ED. None were observed to have syncope; one cocaine-intoxicated patient had a cardiac arrest after a seizure in the intensive care unit, 11 hours after receiving droperidol for extreme agitation in the ED. Despite the limitations of a retrospective study, we believe we found no other evidence of significant cardiovascular events after droperidol.

Since the FDA's black box warning, we have evaluated our use and the safety profile of droperidol in many other circumstances. Between 1997 and 2001, we administered droperidol to 15,374 noncritical patients. We also gave droperidol to 1,172 critical patients (with 396 ECGs; 114 before and after droperidol).[3] Among all of these patients, we detected one clinically significant cardiac dysrhythmia (nonsustained torsades de pointes in a bradycardic alcoholic patient with nausea and vomiting). This patient subsequently underwent electrophysiologic studies with intravenous droperidol administration, with resulting prolongation of the $QT_c$ but no induction of torsades de pointes.

Although we respect the FDA's black box warning, we are puzzled by the information that it was based on. When carefully reviewed, the case against droperidol seems to rest on a few cases of patients receiving the drug in single doses consistent with what we give in the ED.[4] We are curious about the review methods employed by the FDA that have forced a change in clinical practice at some institutions, have led many hospital pharmaceutical committees to spend hours searching for alternative equally effective drugs, and have left some hospital administrators extremely nervous. We question whether the FDA evidence against droperidol is more persuasive than the evidence against haloperidol,[5,6] ziprasidone (Geodon),[7] or other drugs that are known to lengthen the QT interval and cause torsades de pointes but apparently have not yet come under such intense scrutiny. We also question whether there is enough evidence against droperidol to suggest the use of newer, more expensive, and, to our knowledge, no safer drugs than one that has been a long-standing member of our armamentarium. Our experience with droperidol runs counterintuitive to what the FDA apparently has acted on, and our preliminary retrospective studies are not yet convincing us otherwise.

We agree with Dr. Keenan and colleagues that our definition of adverse events did not include QT prolongation and malignant cardiac arrhythmias. Given the nature of our study, the timing of data collection (before the FDA black box warning), and our study purpose, these were not specific study end points. These could not have been measured for most of our patients because no ECGs were obtained. We also agree that the risk-to-benefit ratio should be calculated before the use of this (and any) drug. We disagree that alternative drug classes always should be considered first line for these agitated patients; each has its own potential complications.[4] We leave our conclusions unchanged.—**Michelle Biros, MD, MS** (biros001@umn.edu), *Department of Emergency Medicine, Hennepin County Medical Center, Minneapolis, MN*; and **Peter Chase, MD, PhD,** *Department of Emergency Medicine and Arizona Poison Center, University of Arizona, Tucson, AZ*

## References

1. Herrick IA, Craen RA, Belb AW, et al. Propofol sedation during craniotomy for seizures: patient controlled administration versus neuroleptanalgesia. Anesth Analg. 1997; 84:1285–91.
2. Bissonnette B, Swan H, Ravussin P, Un P. Neuroleptanesthesia: current status. Can J Anesth. 1999; 46:154–68.
3. Martel M, Miner J, Lashkowitz S, Danahy M, Clinton J, Biros M. QT prolongation and cardiac arrhythmias associated with droperidol use in critical emergency department patients [abstract]. Acad Emerg Med. 2003; 10:510–1.
4. Horowitz BZ, Bizovi K, Moreno R. Droperidol—behind the black box warning. Acad Emerg Med. 2002; 9:615–8.
5. Jackson T, Ditmanson L, Brendan P. Torsades de pointes and low dose oral haloperidol. Arch Intern Med. 1997; 157:2013–5.
6. Sharma ND, Rosman HS, Padhi D, Tisdale JE. Torsades de pointes associated with IV haloperidol in critically ill patients. Am J Cardiol. 1998; 81:238–44.
7. Kelly DL, Love RC. Ziprasidone and the QTc interval: pharmacokinetic and phramacodynamic considerations. Psychopharmacol Bull. 2001; 35:66–79.