A Review of the Safety and Efficacy of Droperidol for the Rapid Sedation of Severely Agitated and Violent Patients

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Background: Droperidol had become a standard treatment for sedating severely agitated or violent patients in both psychiatric and medical emergency departments. However, several recent articles have suggested that droperidol may have a quinidine-like effect similar to that of thioridazine in inducing dysrhythmia.

Method: In view of the recent U.S. Food and Drug Administration (FDA) position regarding the use of thioridazine, the authors reviewed the literature regarding droperidol and dysrhythmia in a MEDLINE search for the years 1960–2002 using the search terms *droperidol*, *dysrhythmia*, *QTc interval*, and *sudden death* as well as their own experience in using droperidol in a busy psychiatric emergency department. This review was done before the FDA's very recent and peremptory warning about droperidol.

Results: The authors report that, in treating approximately 12,000 patients over the past decade, they have never experienced a clinically significant adverse dysrhythmic event using droperidol to sedate severely agitated or violent patients.

Conclusion: The authors conclude that, in clinical practice, droperidol is an extremely effective and safe method for treating severely agitated or violent patients. While in theory droperidol may prolong the QT interval to an extent similar to thioridazine, in clinical use there is no pattern of sudden deaths analogous to those that provoked the FDA warning about thioridazine.

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While a host of medications have some degree of quinidine-like effect in prolonging the QT interval, for the most part these medications are quite safe in routine clinical practice.[1–5] However, with the recent concern raised by the U.S. Food and Drug Administration's (FDA) black box warnings about the potential for dysrhythmia from the use of thioridazine,[6] and now droperidol,[7,8] we elected to review the literature on the safety of droperidol, which also has a quinidine-like effect on the QT interval to an extent predicted to be similar to thioridazine,[9] in a MEDLINE search for the years 1960–2002 using the search terms *droperidol*, *dysrhythmia*, *QTc interval*, and *sudden death* and compare those findings with our own clinical experience.

This was especially important to us because we have routinely been using droperidol to sedate violent or severely agitated patients even though it has FDA approval only as an antiemetic and anesthetic. In the face of an adverse event, it would be extremely difficult to defend in court the "off-label" use of droperidol to sedate a violent patient if that medication did not have a well-established record of safety and efficacy. There have been several articles in the literature that recommend the use of droperidol for use in this context,[10–12] even recommending it as superior to haloperidol[13,14] or lorazepam[15] and calling droperidol the "drug of choice for the rapid and reliable control of acute agitation"[16] or for the control of dangerous behavior because of its short latency of onset.[10] However, all of this literature predates the FDA's black box warning and offers little protection from litigation or reassurance to physicians.

According to the FDA, since droperidol was introduced in 1970, the agency has received 100 reports of cardiovascular events worldwide associated with the use of the drug.[17] The American Society of Anesthesiologists report[17] indicated that among a subset of 38 cases for which there were some details available, there were 25 cases of sudden death and 9 of torsades de pointes. Twelve of the adverse events occurred with doses of 2.5 mg or less, including 3 cases of torsades de pointes. Conversely,

another report indicated that there were only 18 cases resulting in death; of those, 6 were directly related to QT prolongation and torsades de pointes, and 5 of the deaths were with doses of 2.5 mg or less.[18] Of these 100 cases, 1 occurred in 2001, and the rest were in previous years. The FDA is not releasing information to the public about these events and is requiring written queries under the Freedom of Information Act (FOIA).[18]

The FDA has not asserted or shown that these events were solely due to droperidol, and not secondary to another illness, medication, or postoperative complication. They have also given no information about the total number of patients treated with droperidol or the total number of doses given these patients. What is the actual risk and compared to what?

In the United Kingdom, Janssen-Cilag, the manufacturer of droperidol in Britain, voluntarily withdrew droperidol from the market "following an extensive risk-benefit assessment,"[19] but risk and benefit to whom? The company reportedly withdrew the oral formulation "to prevent chronic use."[19] Is this about QTc or tardive dyskinesia? With regard to the injectable form, the company concluded it "would no longer be viable." When the company was contacted several times by one of the authors (W.D.M.), their representatives would not elaborate.

The British government's Committee on Safety of Medicines (CSM) has advised physicians that "droperidol can continue to be used for its licensed acute use (to calm manic, agitated patients) while supplies are available, but that no new patients should be given the drug for chronic use. In addition, the CSM says that treatment with droperidol should not be stopped until a suitable alternative has been identified."[20]

One must also ask whether droperidol would have a black box warning today if it were still under patent to a pharmaceutical industry leader. Ziprasidone recently underwent the same scrutiny by the FDA because of QT prolongation, and Pfizer immediately funded a study to show that not only was QT prolongation not clinically significant, but that there is extremely wide natural inter- and intra-individual variability of the QT interval. Ziprasidone, at present, does not have a black box warning.

BACKGROUND

The use of droperidol as a sedative in acutely agitated patients goes back over 30 years in Europe, where it is approved for use as an antipsychotic.[12] Droperidol was initially described in 1963 by Janssen et al. for use as an antimanic agent for agitation.[21] There were reports in the U.S. literature of using droperidol for agitation as early as 1972.[22,23] We started using droperidol as a first-line treatment for severe agitation at our hospital about a decade ago because it is faster acting, shorter acting, and cheaper than the haloperidol that we had been using.

SIDE EFFECT HISTORY

Almost since the time of their introduction there has been an awareness of a potential association between the use of antipsychotic medications and sudden unexplained death.[1,2,24] Historically, this has not been a significant, clinical concern for a variety of reasons. The incidence of this sudden unexplained death is very low, and it most commonly has occurred in the context of an overdose or the use of large doses in critically ill, hospitalized patients.[2–4]

In 1984, Liberatore and Robinson[25] postulated torsades de pointes leading to ventricular fibrillation as the mechanism of action for sudden death associated with neuroleptic drug treatment. Later articles refined the mechanism of action to a dose-related lengthening of the QT interval caused primarily by blockade of cardiac potassium channels.[1,9,26]

A study by Szuba et al.[27] looked at the safety of droperidol both intramuscularly (IM) and intravascularly (IV) in a series of 97 severely agitated inpatients. These patients received a total of 385 doses of droperidol ranging from 2 to 200 mg; 271 doses IM (7.0 ± 2.8 mg) and 114 doses IV (61.6 ± 31.7 mg). There was only 1 cardiac complication in the form of a brief episode of supraventricular tachycardia after the administration of 50 mg of droperidol IV to a 69-year-old woman without a known cardiac history. The authors note that this same patient was later able to tolerate a lower dose of droperidol without complication. These doses are well above our standard dose by an order of magnitude.

Droperidol has been safely used in anesthesiology for years, as an antiemetic, premedication, and even a general anesthetic in a procedure called neuroleptanesthesia. As recently as 1999, the American Society of Health-System Pharmacists recommended droperidol as a safe and cost-effective medication for postoperative nausea and vomiting.[28] In their guidelines, they reference 22 articles that discuss the safety and efficacy of droperidol, representing 2431 patients, ranging in age from ≈ 2 years to 65 years, and doses from 0.182 mg (in children) to 10 mg, with most studies using 1.25-mg doses. In every one of these studies, the patients were monitored in the standard fashion during and after any operative procedure with electrocardiogram and measurements of blood pressure and heart rate, and there was not one clinically significant cardiac event, instance of death listed as a side effect, or adverse event. While the doses used in these studies are not all as high as those we commonly use, they are well within the range mentioned by the FDA as being dangerous.

These studies represent a patient population similar to, if not broader than, that seen in the common psychiatric emergency setting. Studies have tried to determine what patient population is at greatest risk of suffering a clinically significant cardiac event while on an antipsychotic medication that lengthens QT intervals, but to date there has been no well-defined group for whom these medications are dangerous. Buckley and Sanders[9] suggested that the risk of sudden death would be greater in "high-risk populations (elderly, preexisting cardiovascular disease, inherited disorders of cardiac ion channels or of antipsychotic drug metabolism) or of people taking interacting drugs (such as drugs that prolong the QT interval), e.g., tricyclic antidepressants, drugs that inhibit antipsychotic drug metabolism, or diuretics."(p215) While it might seem prudent to use these drugs cautiously in "high-risk populations," this caution is based on very incomplete data according to the authors. Moreover, the same senior author in an earlier study had found that making "adjustments for age, sex, dose ingested, and coingestion of tricyclic antidepressants or lithium had no major effect on the odds ratio observed"(p226) with respect to inducing dysrhythmia, thus undermining the existence of a high-risk population.[29] Moreover, in this same article, Buckley and colleagues[29] reported on ECG changes associated with "neuroleptic poisoning" from many different agents, including thioridazine, chlorpromazine, trifluoperazine, haloperidol, prochlorperazine, and fluphenazine, but not droperidol.

As noted above, several other classes of drugs besides antipsychotics have a quinidine-like action on cardiac repolarization.[1–5] In combination, it is possible that these drugs could act synergistically. There was one report of an interaction between droperidol, the selective serotonin reuptake inhibitor fluoxetine, and the muscle relaxant cyclobenzaprine mediated through the cytochrome P450 drug pathway.[30]

While many neuroleptics have quinidine-like action prolonging the QT interval, 3 agents available in the United States stand out in the literature: thioridazine, droperidol, and haloperidol. Thioridazine and droperidol have been the focus of several articles as particular risks.[9,31,32] Thioridazine has been associated with sudden deaths in case reports for almost 40 years.[24] The risks related to thioridazine have been enough to convince the FDA. But the reports of harm from droperidol in the literature are few indeed.[9] There is not one incident of sudden death secondary to QT prolongation, or torsades de pointes that we have found[4] prior to the FDA's peremptory warning about droperidol.

Now the FDA dictates a black box warning because of 100 adverse cardiovascular events, resulting in either 18 or 25 deaths according to conflicting reports, but no details are available for review without resorting to an FOIA request. An article by Glassman and Bigger[33] also reported that droperidol and haloperidol have been documented to cause sudden death. But haloperidol has no black box warning. Our experience and review of the literature suggest that droperidol is the safer and surely the faster of the 2 drugs in sedating extremely agitated patients. Moreover, Glassman and Bigger described only 10 to 15 adverse events in 10,000 person-years of observation with respect to droperidol.[33]

While there have been numerous studies to show that QT lengthening occurs in patients who are given antipsychotics, there have been no articles showing a clinical manifestation of this lengthening into torsades de pointes or deaths. Reilly et al.[31] studied 101 healthy reference subjects and 495 psychiatric patients. They suggested that antipsychotic drugs caused a dose-related lengthening of QT interval and that "the risks are substantially higher for thioridazine and droperidol."(p1048) They concluded "these drugs may therefore confer a risk of drug-induced arrhythmia."(p1048)

Gury and colleagues[32] in a recent article from France reported that, of the many antipsychotics available in the United States, thioridazine and droperidol carry a high risk of arrhythmia due to their effect on QT interval, and haloperidol and chlorpromazine a lesser risk. However, these conclusions were based on studies of the propensity of an individual drug to lengthen the QT interval and not based on empirical evidence of reports of actual dysrhythmias in patients who had received the drugs. Moreover, these studies tended to be based on doses that were much higher than those routinely used to sedate patients in the emergency department setting.

For example, another study done in France gave 0.25 mg/kg of droperidol intravenously to 55 unselected patients and found that 70% experienced a "significant prolongation of the QT interval by the end of the first minute,"(p543) which could favor the onset of torsades de pointes.[34] In the standard 70-kg male, that would be a dose of 17.5 mg of droperidol, far more than we have ever given a patient in our emergency room. However, other authors were unable to demonstrate a dysrhythmia-triggering effect after intravenous injection of 12.5 mg of droperidol in a patient suffering from a congenital prolongation of the QT interval.[35] The fact that the droperidol was given intravenously is of some concern, though the absorption of intramuscular droperidol is so rapid that response is "almost equivalent to that observed following intravenous administration."36(p365)

Conversely, haloperidol has been the subject of a series of articles and case reports as actually causing torsades de pointes.[37–46] With 2 exceptions,[45,46] these articles reported on critically ill medical or surgical patients who had been given extremely large doses of haloperidol intravenously, usually to control an agitated delirium. This was consistent with Lawrence and Nasraway's report[4] on 18 critically ill

patients who developed conduction disturbances after large intravenous doses of butyrophenone.[4] In that series, 16 patients had received haloperidol and 14 of these developed torsades de pointes. But neither of 2 patients given droperidol developed torsades de pointes.[47] One droperidol patient, a 34-year-old man, received 19 mg of droperidol in 24 hours and developed supraventricular tachycardia with premature ventricular contractions in the context of underlying aortic valve disease. His corrected QT interval (QTc) extended from a baseline of 400 msec to a maximum of 476 msec. The other patient, a 54-year-old man, received 480 mg of droperidol in 24 hours, and his QTc extended from a baseline of 437 msec to a maximum to 560 msec. He did develop a first-degree atrioventricular block and he suffered an acute myocardial infarction. According to a report by Bednar and colleagues,[48] torsades de pointes rarely occurs with a QTc of less than 500 msec, which is consistent with the report by Lawrence and Nasraway.[4] The patient given droperidol whose QTc reached a maximum of 560 msec would seem to have been at risk to develop torsades de pointes, yet he did not.

The concern about QT prolongation with droperidol treatment has been based more on a theoretical prediction of torsades de pointes rather than on an empirical, clinical record of actually having frequently caused torsades de pointes. The important factor to remember while interpreting these studies is that the QT interval prolongation is dose dependent,[49] and in the doses typically used in emergency departments for sedation, droperidol is quite safe. The proof of this idea is reflected in case reports and studies of its clinical use.

OUR EXPERIENCE

We have used a combination of droperidol, 5 mg, and lorazepam, 2 mg, intramuscularly in severely agitated or violent patients for the last 10 years. We have detailed medication records back to October 1, 1998. Between October 1, 1998, and May 14, 2001, we gave 4145 five-mg doses of droperidol in our emergency department and our acute inpatient service; no single dose exceeded 5 mg. That averages 133 doses a month. We routinely monitor vital signs for at least an hour after administration of the medication, but we do not routinely use a cardiac monitor. If we conservatively use 100 patients per month as our rate for the entire decade, that yields an estimate of more than 12,000 patients treated with intramuscular droperidol in the last decade.

In all that time, we have not had a single case of clinically significant dysrhythmia (as distinguished from transient hypotension, see below). As we do not routinely use a cardiac monitor, we cannot be certain that there were no episodes of subclinical dysrhythmia, but torsades de pointes would be unlikely to be subclinical. This was an unselected group of patients representing the entire spectrum of problems that present to a psychiatric emergency department. We do know that the mean age of the patients who were seen in our emergency department was 35.5 years for 1999–2000. By regulation, we may not see anyone younger than 18, and we tend to see very few people over age 65 because they almost universally have insurance and are not often brought to us. Our record-keeping system is not organized to access that kind of demographic information.

While we occasionally see transient decreases in blood pressure in patients of any age, we feel this is most likely due to droperidol's action as a weak α-blocker that can cause postural hypotension. We have had only a single adverse hypotensive event occur when using droperidol. This was in a diabetic 71-year-old male patient who was intoxicated (blood alcohol level = 0.20 with weak effort on the Breathalyzer [Alco-sensor III, Intoximeter, St. Louis, Mo.]), quite agitated, and threatening. The patient was also found to have hypertension, peripheral vascular disease, bladder cancer under observation, and a history of a prior myocardial infarction. His medications included digoxin, 0.125 mg once daily; diltiazem, 120 mg once daily; furosemide, 20 mg once daily; metoprolol, 50 mg q.h.s.; lisinopril, 20 mg once daily; atorvastatin, 10 mg once daily; alprazolam, 0.25 mg b.i.d.; and aspirin, 325 mg once daily His insulin regimen was human insulin 70/30, 52 units daily. The patient was given 2.5 mg of droperidol intramuscularly for his severe agitation, but it was impossible to get a baseline blood pressure reading. He was also given thiamine, 100 mg, and lorazepam, 1 mg, intramuscularly. His vital signs were to be monitored every 15 minutes. His pulse was always strong, regular, and about 100 b.p.m. His first blood pressure reading was obtained at about 5 minutes after being given medication and was 100/70 mm Hg. About 15 minutes later, the patient was sedated, but conscious and cooperative. His pulse was still strong and regular at 100 b.p.m., but his blood pressure was 70/40 mm Hg. He was placed in a Trendelenburg position and his blood pressure immediately rose to 100/70 mm Hg. He remained conscious throughout this time and his pulse remained regular. It would be difficult to say with certainty whether droperidol was the primary or even a significant factor in this patient's hypotensive episode. But the episode did quickly resolve with rehydration and is consistent with droperidol's α-blocker effect. With regard to our overall experience, this patient stands out as unique. Given the patient's age and blood alcohol level, the lorazepam was relatively contraindicated, though the record does indicate that he was extremely agitated.

DISCUSSION

No medicine is without risk, but violent and severely agitated patients are at risk to hurt themselves or others if left untreated. Droperidol was introduced in 1970, and the FDA claims 18 or 25 deaths but offers no risk/benefit analysis. How many patients received droperidol in that time, hundreds of thousands, millions? How many of these patients would have had adverse events if given placebo or nothing at all? Our experience with droperidol has been dramatically different from the problems predicted by the FDA due to droperidol's propensity to prolong the QT interval, which suggested that droperidol would be very like thioridazine. And this experience seems consistent with the experience of others as reflected in the literature. When the FDA issued its warning on thioridazine, Timell[50] published a risk/benefit analysis. He found that while the risk of sudden death from thioridazine was very low, given the large number of similarly effective alternatives, the warning was justified. Our experience and review of the literature do not support a similar conclusion regarding droperidol. The single most commonly used alternative, haloperidol, has at least the same QT prolongation risks and is both slower in onset and longer in duration of action.

We suspect that had droperidol not been an orphan drug but rather had been "on patent" to a pharmaceutical industry leader that the FDA would have acted more deliberately and been more forthcoming about their supporting data. It would have been a story more akin to that of ziprasidone. We think that the FDA was precipitous to issue their warning on droperidol without the opportunity for public discussion.

Ironically, the first atypical antipsychotic to reach the market in an injectable form will be ziprasidone. This is a medication that has barely finished its clinical trials in its injectable form and has some propensity to prolong QTc in its oral form. Droperidol, on the other hand, is a medication with 100 adverse cardiovascular events worldwide after 3 decades of use in untold numbers of patients. But it is an orphan drug.

Ziprasidone will surely be much more expensive than droperidol. Will it be as fast in onset and short in duration? And most importantly in the long run, will it be as safe? As Glassman and Bigger have recently written, "Only widespread use will prove if ziprasidone is entirely safe."[33(p1174)] But what drug in history has been entirely safe? These authors note that, "To date, all antipsychotic drugs have the potential for serious adverse events. Balancing these risks with the positive effects of treatment poses a challenge for psychiatry."[33(p1174)]

CONCLUSION

On the basis of 10 years' experience and our review of the literature, we feel that droperidol is a very safe drug for use as a sedative in acutely agitated or violent patients in an emergency department setting when used in 5-mg intramuscular doses, with or without lorazepam. While this is an "off-label" use, we feel that droperidol's safety and efficacy justify its use in this setting.

Drug names: alprazolam (Xanax and others), atorvastatin (Lipitor), chlorpromazine (Thorazine and others), cyclobenzaprine (Flexeril), digoxin (Lanoxin, Lanoxicaps, and others), diltiazem (Cardizem, Tiazac, and others), droperidol (Inapsine), fluoxetine (Prozac and others), fluphenazine (Prolixin, Permitil, and others), furosemide (Lasix and others), haloperidol (Haldol and others), human insulin (Humulin), lisinopril (Zestril, Prinivil, and others), lorazepam (Ativan and others), metoprolol (Lopressor and others), prochlorperazine (Compazine and others), trifluoperazine (Stelazine and others), ziprasidone (Geodon).

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