Abstract—Droperidol is an antipsychotic and antiemetic drug that has been used extensively by Emergency Physicians, Psychiatrists, and Anesthesiologists worldwide since 1967. It also has been used effectively for other diverse conditions, such as treatment of headache and vertigo. As of January 2001, Droperidol was no longer available in Europe after its founder, Janssen-Cilag Pharmaceuticals, discontinued its distribution. In December 2001, the United States Food and Drug Administration (FDA) placed a black box warning on the use of Droperidol in response to an association between Droperidol and fatal cardiac dysrhythmias, such as torsade de pointes, resulting from prolongation of the QT interval. In this review we closely examine the pharmacology, indications, use, and complications associated with Droperidol, and speculate on its future use in the Emergency Department. © 2003 Elsevier Inc.

Keywords—Droperidol; Inapsine; antipsychotic; Emergency Department; FDA warning

INTRODUCTION

Droperidol is a butyrophenone, a class of antipsychotic agents that include Haloperidol, and is marketed in the United States under the trade name Inapsine™. Butyrophenones were initially studied in the late 1950s at the Janssen laboratories in Belgium as a potential substitute for Morphine (1). It was soon realized this class of drugs was more useful in the treatment of psychosis, and Haloperidol was the first agent to be approved for this use in 1957 (1). Droperidol has been used extensively for the past 30 years by Psychiatrists, Emergency Physicians, and Anesthesiologists. Recently, however, the drug has come under intense scrutiny for its role in prolonging QT intervals and development of fatal cardiac dysrhythmias (2,3). The Medicines Control Agency of the United Kingdom initially raised a safety concern regarding the chronic use of high-dose Droperidol in psychiatric patients. This may have led its founding firm, Janssen-Cilag Ltd of Belgium, to discontinue production and distribution of Droperidol to most of the world as of January 2001 (4,5). This resulted in an outcry from physicians in Europe, mainly anesthesiologists, who used Droperidol extensively for postoperative nausea and vomiting (PONV) and remarked on its efficacy, low cost, patient satisfaction, and excellent safety profile (4–6).

In December 2001, the United States Food and Drug Administration (FDA) issued a “black box warning” (Appendix), its most serious alert, on the use of Droperidol (7). The Canadian Health Protection Branch followed soon thereafter (8). Before these warnings, doses greater than 25 mg were considered to put patients at higher risk of QT prolongation and dysrhythmia, and it was estimated Droperidol constituted 30% of the antiemetic mar-
ket, with over 25 million units sold in 2000 (9). North American Anesthesiologists, Pharmacists, and Emergency Physicians reacted skeptically to these new restrictions on the use of Droperidol (9–13). Now Emergency Physicians (EPs) who still have access to Droperidol must decide the risk/benefit ratio for its use in their particular practice. To aid in this decision, in this article we extensively review the current and past literature regarding Droperidol and its potential for adverse drug reactions in the Emergency Department (ED).

**PHARMACOLOGY**

Butyrophenones, of which Droperidol is a member, are potent dopamine (D) antagonists with less potent α receptor effects. Droperidol binds preferentially to the D-2 and α-1 receptors, respectively (1). Both its antiemetic and antipsychotic properties derive from this potent D-2 antagonism. Unlike the phenothiazines, butyrophenones have weaker anticholinergic and antihistaminic properties, and greater tendency to produce extrapyramidal side effects. Structurally (Figure 1), butyrophenones are similar to γ-aminobutyric acid (GABA) and are concentrated in the central nervous system (CNS) (1). This may account for their potent tranquilization properties, in which a quiescent state with reduced motor activity, anxiety, and apprehension is achieved with low to moderate doses (14). During this sedation, the patient is responsive to commands and is usually indifferent to his or her surroundings. There is evidence Droperidol inhibits specific GABA and nicotinic receptors in high doses, which may explain the anxiety, dysphoria, and akathisia that accompanies high doses in certain patients (15).

Droperidol is the shortest acting of the butyrophenones, with a half-life of 2 h (16). Peak serum levels occur 1 h after intramuscular (i.m.) and intravenous (i.v.) injection, and it is widely protein bound with a volume of distribution of 2 L/kg. Droperidol may be administered orally, i.m., and i.v. Typical antiemetic doses range from 0.625 to 2.5 mg i.v./i.m., and doses for chemical restraint begin at 5 mg i.v./i.m. and higher. It readily crosses the blood-brain barrier and is distributed into the cerebrospinal fluid (17). It slowly traverses the placenta, and it is unclear if it is present in breast milk (17). It is extensively metabolized in the liver, and excretion is primarily renal (75%) with the remainder excreted in the feces. Its metabolites, benzimidazolone, p-fluorophenylacetic acid, and p-hydroxypiperidine, are inactive. Roughly 10% is excreted in the urine unmetabolized (18,19).

**INDICATIONS**

The most common indications for Droperidol use in the ED are for chemical restraint of acute psychosis and agitation, and for antiemesis (20,21). Of interest, Droperidol has received FDA approval for only two indications, as an antiemetic and as an anxiolytic/amnesic agent before diagnostic or surgical procedures for children and adults. Droperidol is a powerful and inexpensive antiemetic, as demonstrated by several studies (21–29). However, it does not have FDA approval for hyperemesis gravidarum and chemotherapy-induced nausea and vomiting, despite several studies demonstrating its efficacy when compared to other alternative antiemetics (28,29).

Perhaps the most important use of Droperidol in the ED is rapid tranquilization of the violent, agitated patient (20). A plethora of studies has proven the efficacy of Droperidol for this particular indication, especially when compared to other agents, such as benzodiazepines (30–37). Furthermore, Droperidol has been effective for treating all subsets of agitation, including stimulant abuse, head injury, mania or psychosis, and in pediatric patients (35–37). Unlike Haloperidol, Droperidol has never received FDA approval for use in treatment of acute psychosis.

Droperidol, originally synthesized as a potential alternative to Morphine, also has been used for atypical pain syndromes. Before the FDA warning, Droperidol had become increasingly popular for treatment of headache.
Droperidol has several CNS side effects that have been previously described. Dysphoria, drowsiness, hallucinations, shivering, and anxiety have been reported after Droperidol injection, but are uncommon (49,50). Extrapyramidal side effects from Droperidol’s action on the D-2 receptor include akathisia and dystonias, such as torticollis, and oculogyric crisis (49–51). Neuroleptic malignant syndrome after Droperidol administration has been described in patients on long-term antipsychotics, such as Lithium and phenothiazines, and during elective surgery under anesthesia (52–55). The risk of Droperidol lowering threshold for seizure seems to be a common dogma, but there is little evidence for its support in the form of case reports or controlled studies (51). One study in mice demonstrated low to moderate doses of Droperidol lowered seizure threshold, whereas high doses paradoxically raised it (56). A report from Russia noted tonic episodes resembling seizures in patients after receiving Droperidol and Haloperidol (57).

One of Droperidol’s most important advantages is its lack of respiratory depression even in high doses (58). Only one case of respiratory distress has been described after 5 mg i.v. Droperidol was given to a patient suffering from lysergic acid (LSD) toxicity who had been taking Lithium and Risperidone (59). After becoming rigid and unable to self-ventilate, he was intubated. It was postulated by the authors that Droperidol may have induced serotonin syndrome in this patient. Angioedema, laryngospasm, and true allergic reactions have been reported with Droperidol, but these phenomena seem to be very rare events (60,61). Agranulocytosis was reported in two patients after addition of Droperidol to an existing phenothiazine regimen, but no further reports exist (62).

ADVERSE DRUG EFFECTS: CARDIAC

After administration of Droperidol, tachycardia and mild hypotension, presumably from α-1 antagonism, have been reported, but these side effects are extremely rare (63–65). Decreased left ventricular end diastolic pressure, but not cardiac contractility or systemic vascular resistance, was noted after i.v. Droperidol administration in a study of nine patients (66). Droperidol’s effects on the ionic currents of the heart were recognized by Hauswirth in 1967 and by Kern and associates in 1971 (67,68). This was followed by several studies that further defined Droperidol’s site of action (69–77). The process of repolarization of cardiac cells involves sodium, calcium, and several different potassium channels (Figure 2). Droperidol and many other antipsychotics drugs seem to delay repolarization of ventricular cells by blocking a specific type of channel, the potassium rectifier (Ikr) channel (2.78,79). This is represented by QT interval prolongation on the electrocardiogram (EKG).

Corrected QT intervals less than 440 ms in duration are considered normal, and intervals greater than 500 ms are considered high risk (80). Torsade de pointes is a unique polymorphic ventricular dysrythmia associated with a long QT interval, which is usually unresponsive to standard antidysrhythmic drugs (81,82). It exists in a primary congenital form, and in a secondary form that is most often drug induced (80). Treatment of torsade de pointes typically involves i.v. magnesium and possibly cardioversion or cardiac pacing. Other risk factors include hypomagnesemia, hypokalemia, pre-existing dysrhythmia, history of cardiac or liver disease, or concomitant use of drugs known to inhibit hepatic metabolism of Droperidol (7). In a study of 55 patients, Guy and colleagues injected 0.25 mg/kg i.v. Droperidol and noted prolongation of the QT interval in 70% of subjects after 1 min (83). No one developed torsade de pointes in their study, but they recommended caution with administration of Droperidol. Reilly and associates compared EKGs between patients taking antipsychotics and healthy subjects (84). Abnormal QT interval was associated with older age, use of tricyclic antidepressants, Thioridazine, Droperidol, or high doses of any antipsychotic. Lischke et al., in a series of 40 patients injected with increasing dosages of Droperidol, determined a direct association between dose and QT interval prolongation (85).

In their review of antipsychotics, Glassman and Big-
ger emphasized that most members of this class of drugs cause QT interval prolongation (2). Many other drugs that prolong the QT interval, such as Amiodarone, are rarely associated with torsade de pointes (Table 1). Conversely, quinidine is more frequently associated with torsade de pointes despite less QT interval prolongation (2). The phenothiazine Thioridazine, in particular, seems to be the most dangerous of the antipsychotics for the production of torsade de pointes and sudden death (81). These dysrhythmias seem to be more pronounced in elderly patients with heart disease, patients who smoke, and patients on multiple medications. The risk of sudden death from antipsychotic drug use was estimated by Ray and associates in their study of half a million subjects over 2.5 years (86). Their calculation was 11 sudden cardiac deaths per 10,000 person-years in subjects without cardiac disease, or 2.39 times greater risk of death than patients not taking antipsychotics. To date there have been over 100 reports of cardiovascular events attributed directly to Droperidol reported to the FDA, including 20 cases of torsade de pointes, nine cardiac arrests, and two deaths at doses of 2.5 mg i.v. or less (11).

Although evidence exists that Droperidol causes prolongation of the QT interval based on the aforementioned studies, it is difficult to ascertain whether Droperidol alone is at fault for the genesis of subsequent dysrhythmias, as patients who receive the drug often have concomitant medical and psychiatric problems. Many case reports describe patients undergoing elective and emergent surgery in the operating room under general anesthesia (88–91). Many of these patients also may have been taking cardiac and psychotropic medication. For instance, a recent case report involves a patient with chronic renal failure on hemodialysis who underwent a total hysterectomy under general anesthesia and developed a chaotic ventricular dysrhythmia (89). Another series involved three critically ill patients with esophageal varices receiving vasopressin and nitroglycerin (90). The influence of general anesthetic agents combined

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**Table 1. Drugs That Prolong QT Interval or Induce Torsade de Pointes**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Amiodarone (Cordarone™)</td>
<td>Indapamide (Lozol™)</td>
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<tr>
<td>Bepridil (Vascor™)</td>
<td>Isradipine (Dynacirc™)</td>
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<td>Chlorpromazine (Thorazine™)</td>
<td>Levofloxacin (Levaquin™)</td>
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<td>Cisapride (Propulsid™)</td>
<td>Levomethadyl (Orlaam™)</td>
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<td>Clarithromycin (Biaxin™)</td>
<td>Mesoridazine (Serenil™)</td>
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<td>Desipramine (Norpramin™)</td>
<td>Moxipril/HCTZ (Uniretic™)</td>
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<tr>
<td>Dolasetron (Anzemet™)</td>
<td>Moxifloxacin (Avelox™)</td>
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<td>Disopyramide (Norpace™)</td>
<td>Naratriptan (Amerge™)</td>
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<tr>
<td>Dofetilide (Tikosyn™)</td>
<td>Nicardipine (Cardene™)</td>
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<tr>
<td>Dopexin (Sinequan™)</td>
<td>Octreotide (Sandostatin™)</td>
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<td>Zonalon™</td>
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<td>Erthromycin (Erythromycin™)</td>
<td>Paroxetine (Paxil™)</td>
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<td>Feibamate (Felbrol™)</td>
<td>Pentamidine (Pentam™)</td>
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<td>Flecaidine (Tambocor™)</td>
<td>NebPent™</td>
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<tr>
<td>Fluoxetine (Prozac™)</td>
<td>Probenecid (Lorcip™)</td>
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<td>Foscarinet (Foscavir™)</td>
<td>Procainamide (Procan™)</td>
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<tr>
<td>Fosphenytoin (Cerebyx™)</td>
<td>Procainamide (Procan™)</td>
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<td>Pronestyl™</td>
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<td>Halofantrine (Haldol™)</td>
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<td>Salmeterol (Serevent™)</td>
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<td>Ibutilide (Corvert™)</td>
<td>Sertraline (Zoloft™)</td>
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<td>Imipramine (Tofranil™)</td>
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<td>Sparfloxacin (Zagam™)</td>
<td>Venlafaxine (Effexor™)</td>
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<td>Sumatriptan (Imitrex™)</td>
<td>Ziprasidone (Geodon™)</td>
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<td>Thioridazine (Mellaril™)</td>
<td>Zolmitriptan (Zomig™)</td>
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<td>Tizanidine (Zanaflex™)</td>
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* associated with prolonged QT and torsade de pointes.  
† associated with torsade de pointes only.

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**Figure 2.** Types of receptors involved in the cardiac action potential and ionic flow. (a) Surface electrocardiogram. The QT interval is measured from the beginning of the QRS complex to the return of the T wave to the isoelectric baseline. (b) Action potential showing the four phases of cardiac depolarization and repolarization with the various sites of the ion channel effects. $I_{CaL}$ = L-type calcium channel; $I_{CaT}$ = T-type calcium channel; $I_{Na}$ = depolarizing sodium channel; $I_{K1}$ = inwardly rectifying potassium current; $I_{Kv}$ = rapidly activating delayed rectifier potassium current; $I_{Kr}$ = slowly activating delayed rectifier potassium current; $I_{Kur}$ = ultra rapidly activating delayed rectifier potassium current. (c) Ion current directions during activation of various ion channels. EC, extracellular; IC, intracellular. (Reprinted with permission, Buckley NA, Sander P. Cardiovascular adverse effects of antipsychotic drugs. Drug Saf. 2000;23:218. © 2000 Adis)
with Droperidol on development of dysrhythmias is unclear (92). One study reported no dysrhythmias in a group of patients receiving Enflurane and Droperidol for surgery compared to those receiving Enflurane and Hyoscine (0 vs. 4.4%, respectively) (93). Furthermore, patients requiring Droperidol may already be under the influence of stimulants such as Methamphetamine and Cocaine, which are already prodysrhythmogenic (94). In their review of case reports involving Droperidol and Haloperidol, Lawrence and Nasraway found 11 reports of 18 patients with conduction disturbances linked to butyrophenone use. Thirteen (72%) had a history of cardiovascular disease (82). Of interest, Haloperidol does not have a black box warning by the FDA, even though it has the same cardiac effects as Droperidol and has been associated with torsade de pointes (95). To date, no case reports involving cardiac dysrhythmia and Droperidol have appeared in Emergency Medicine journals.

The promise of improved patient safety with second generation antipsychotics such as Olanzapine, Risperidone, Ziprasidone and Quetiapine has been questionable (78,81,86). Their safety profile may not be fully known until these drugs have achieved widespread use, as exemplified by Sertindole, which was withdrawn after being linked to 12 sudden deaths in Europe (2). The newer antipsychotics also affect the QT interval, and most are not available in an injectable form, thus limiting their use in an acute care setting (96). The same situation seems to apply to antiemetic drugs, as the newer serotonin antagonists, such as Dolasetron, seem to affect the QT interval as well and are considerably more expensive than Droperidol (97).

CONCLUSION

For the past 3 decades, Droperidol has proven to be an excellent antipsychotic and antiemetic agent with an extensive history of use in the ED. It also has been effectively utilized for headache and spinal-cord-mediated pain syndromes, as well as for suppression of vertigo. It is inexpensive, rapid acting, efficacious, and has a short half-life. Droperidol does not cause respiratory depression even in high doses, and has equivalent i.m. and i.v. dosing. Despite the powerful advantages of Droperidol, the risk of prolonged QT interval and torsade de pointes does exist. Furthermore, it seems many other unrelated drugs have this risk as well (Table 1) but most do not carry an FDA black box warning.

There are several alternative drugs available to the Emergency Physician for treatment of nausea and emesis, but far fewer for the control of psychosis and agitation. It seems likely that Haloperidol will also receive a black box warning from the FDA given its current focus on adverse reactions. To avoid any risk of QT interval prolongation, the Emergency Physician is essentially left with benzodiazepines and barbiturates as the only alternatives for sedation. Although the FDA has recommended continuous cardiac monitoring for patients receiving Droperidol, our review demonstrates this may be an overstatement of the risk. Although patients at higher risk for cardiac events, such as those with prior history of dysrhythmia and those receiving high doses of Droperidol, warrant consideration of continuous cardiac monitoring, many low-risk patients receiving small doses may not require continuous cardiac monitoring. For those clinicians who have come to rely on Droperidol and choose to continue using it, we recommend careful patient selection and screening for high-risk individuals, adherence to the FDA guidelines, and continuous cardiac monitoring of the high-risk patient after administration. An understanding of the potential complications of Droperidol use, such as dystonia, torsade de pointes, and their treatments, will ultimately reduce potential liability and increase patient safety.

REFERENCES


Dropéridol in the ED

APPENDIX

WARNING

Cases of QT prolongation and/or torsades de pointes have been reported in patients receiving INAPSINE at doses above those recommended for use. 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, Contra-indications, 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 benzodiazipines, volatiles, anesthetics, and IV opiates. Droperidol should be initiated at a low dose and adjusted upward, with caution, as needed to achieve the desired effect.