# Clinical Practice Statement

## **Safety of Droperidol Use in the Emergency Department** (9/7/2013)

Authors: Jack Perkins, MD FAAEM

Jeffrey Ho, MD FAAEM

Reviewers: Mitchell Heller, MD FAAEM

Lisa Mills, MD FAAEM

Amandeep Singh, MD FAAEM

Zachary Soucy, DO

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Droperidol (Inapsine®) is a butyrophenone used in emergency medicine practice for control of psychosis/agitation (1), as an antiemetic (2), for vertigo (3), as an adjunct analgesic (especially in opioid-tolerant patients) and as a treatment for benign headache (4). Initially produced in 1961, it has numerous sites of biochemical activity, most notably as a dopamine receptor antagonist (D2). It is injectable as an intravenous (IV) and intramuscular (IM) medication giving it utility when dealing with physically resistive patients where IV access may be dangerous or impossible (5). Described dosages used in practice range from 0.625 mg IV for control of nausea to much larger for control of violent agitation (10 mg IM).

### Executive Summary

1. Droperidol is an effective medication in the treatment of nausea, headache, and agitation.
2. The FDA black box warning is not supported by the literature for doses < 2.5 mg.
3. We do not recommend mandating an electrocardiogram (EKG) or telemetry monitoring for doses < 2.5 mg given either IM or IV.
4. Intramuscular doses of up to 10 mg of droperidol appear to be as safe and as effective as other medications used for sedation of agitated patients.

The most common side effects of droperidol are extra-pyramidal such as dystonia or akisthesia, and are dealt with through administration of an H2-blocker such as diphenhydramine. Practitioners may elect to prophylactically administer an H2-blocker prior to droperidol. In 2001, the US Food and Drug Administration (FDA) issued a black box warning for droperidol over concerns of QT prolongation and the potential for torsades de pointes. The FDA stated that an EKG should be obtained prior to droperidol administration and it should not be used if the QTC is > 440 ms in males or > 450 ms in females. The FDA also recommended cardiac monitoring for 2-3 hours after droperidol administration. Clinicians familiar with droperidol in practice have questioned this warning because most of the case reports of torsades de pointes occurred with large doses of droperidol rarely used in the ED setting (25mg-600mg). The FDA warning was a result of 273 adverse event communications (74% of these sent in from outside the U.S.), with only five of these events related to doses of less than 2.5 mg (6). In fact, in the year 2000, over 25 million unit doses of droperidol were sold and only 10 adverse cardiac events were related to doses of 1.25 mg or less (3). All ten of these events had confounding factors that could have explained the cardiac event such as pre-existing cardiac disease or alcoholism. Kao, et al. published on this topic and describe 9 cases of torsades de pointes in 30 years of droperidol use (7).

Droperidol has been studied in numerous clinical settings although the most extensive literature is in the area of chemical restraint, antiemetic use, and treatment of acute headache. The 2010 DORM study looked at droperidol

versus midazolam for sedation of the patient with acute agitation (8). They randomized 91 patients to droperidol, midazolam, or a combination of the two medications. No significant adverse events occurred despite a 10 mg dose of intramuscular (IM) droperidol. EKGs were performed after sedation was achieved and QT prolongation was noted in 2 out of 31 droperidol patients and 2 out of 29 midazolam patients. A 2006 study (153 patients) also evaluated droperidol and midazolam for the acutely agitated patient (9). The authors used 5 mg IV of midazolam or 5 mg IV of droperidol every 5 minutes until adequate sedation was achieved. The median doses required for sedation were 5 mg for midazolam and 10 mg for droperidol. Three patients required active airway management including one patient who required intubation. All three of these patients had received midazolam. Most patients (106/153) had an EKG performed within 30 minutes of sedation and only 3 patients had a QTC > 500 ms and two of those were in the midazolam group. The median QTC for droperidol patients was 439 ms.

In 2001 droperidol was studied in comparison to prochlorperazine for acute headaches in the ED (4). Patients were randomized to 5 mg IM droperidol, 2.5 mg intravenous (IV) droperidol, or 10 mg of prochlorperazine (IM or IV). Droperidol patients received more relief for their headaches and did not suffer any significant side effects. The authors did not obtain EKGs before or after the administration of medications. A similar study was conducted in 2004 by Weaver et al using 2.5 mg of droperidol IV versus 10 mg of prochlorperazine IV (10). They found similar efficacy between the two medications with no significant side effects. Again, no EKGs were obtained in this study.

The prevailing theory regarding the FDA "Black Box" warning is that there were a few isolated cases involving exceedingly large doses of droperidol that resulted in torsades de pointes but that lower doses used in the emergency department pose little if any danger to the patient. In support of this the FDA Anesthetic & Life Support Drugs Advisory Committee stated in 2003:

"The boxed warning really is not about doses of droperidol less than 2.5 mg because the use of droperidol at doses less than 2.5 mg is off-label. We don't have data submitted to the agency to make a determination of safety and efficacy at less than 2.5 mg, and we really are not making any statement about the safety or lack of safety of droperidol at those doses." (3)

When considering emergency physicians frequently employ other medications that also may prolong the QT interval (e.g. ondansetron, azithromycin), it seems unreasonable to obtain EKGs in all patients whenever administering any medication that could prolong the QT interval. We conclude that droperidol is an effective medication that has multiple clinical purposes in the ED, and when used at lower doses (< 2.5 mg), there is insufficient literature to support routine EKGs and telemetry monitoring. We further recommend a clarification of the FDA black box warning to address the dosage of droperidol in regards to their recommendation.