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Use of Droperidol in the Emergency Department

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The purpose of this policy statement is to reaffirm the safety and efficacy of droperidol for a variety of common conditions treated in emergency departments (EDs). Multiple studies show droperidol's superiority to a variety of other drugs for the following conditions: nausea, vomiting, headache, or undifferentiated agitation. Due to a black box warning along with subsequent drug shortage, use of droperidol was severely curtailed. However, with recent increased availability, along with recently published safety data, we believe that this unique drug should have its black box warning removed and be promoted for use in the ED when clinically indicated.

Droperidol is a butyrophenone with an approved indication for reducing the incidence of nausea and vomiting associated with surgical and diagnostic procedures (see package insert, American Reagent, 2019).[1] It has also been commonly used for control of chemotherapy-induced nausea and vomiting, treatment of migraine headaches, and sedation of agitated psychosis. Its side effects include sedation, extrapyramidal disorders (akathisia), orthostatic hypotension, and prolongation of QT in a dose-dependent fashion.

In 2001, the FDA released a black box warning describing the risk of QT prolongation and torsades de pointes.[2] The warning states that QT prolongation has occurred in patients without known risk factors and in some cases has been fatal. The warning goes on further to state that this drug should be reserved for use only when other acceptable treatments have not provided an adequate response and recommends that all patients have a 12-lead ECG prior to administration and if any QTc prolongation exists, to avoid droperidol. It also recommends that ECG monitoring continue for 2 to 3 hours post administration.[1] Because of this warning, many states and hospitals limited droperidol's use to low doses intramuscularly, or banned its use altogether, especially in the absence of concurrent cardiac monitoring or pre-administration electrocardiogram (EKG). Subsequently, and despite a lack of concern from clinicians, the black box warning abruptly curtailed the use of a safe and effective drug in US hospitals.[3]

Since the addition of the black box, the justification for its widespread application has been called into question. The FDA based its warning on 65 case reports submitted regarding adverse cardiac events from droperidol, the majority at extremely high doses (25 to 250 mg), higher than typically used in the US therapeutically.[4-6] At low doses, <2.5 mg, there were only 10 adverse cardiac-related events, and 2 deaths, all with confounding factors.[5,7] Furthermore, a review of the FDA's medical product safety reporting program for health professionals, MedWatch, from the time period 1997 to 2002 when use was widespread, revealed only 89 deaths, with a minority in the United States. Five of these deaths involved exposure to doses of ≤2.5 mg.[8] Eventually, the FDA conceded that the black box warning does not apply for doses of droperidol less than 2.5 mg.[9] Since that time, droperidol use has been studied in thousands of ED cases without any occurrence of fatal dysrhythmias, with dosing in many cases over 10 mg.[10,11]

Multiple trials published since the black box warning confirm the safety and potential superiority of low-dose droperidol for the treatment of nausea and vomiting in the ED.[12] A study of ED patients presenting with nausea, showed that droperidol (1.25 mg IV) reduced symptoms better than metoclopramide or prochlorperazine (change in nausea on 100 mm visual analog scale, –54.5 mm vs –40.2 mm vs –40.5 mm), with the only adverse effect being self-reported restlessness or anxiety at 24-hour follow-up (71% vs 25% vs 35%) with over 90% satisfaction regardless of group.[13] Another study indicated less emesis when compared to ondansetron in the first 2 hours postoperatively.[14] A more recent ED study showed no increase in restlessness or agitation with droperidol (1.25 mg IV) vs metoclopramide or ondansetron. Although underpowered, the study reported that patients who subjectively "achieved the desired effect" were statistically higher in the droperidol group than in the placebo group (77% vs 59%; ARR=18%; 95% CI 3 to 33%; NNT=5) and less rescue medication was required.[12] In a recent Cochrane review, the only antiemetic to show a significant decrease in nausea was droperidol.[15]

Droperidol has been used for many years for the safe treatment of headaches in the ED. Droperidol at 2.5 mg IV was found to be superior to prochlorperazine at 10 mg IV for migraine control.[16] Doses of IM droperidol up to 8.25 mg IM were superior to placebo for migraines without inducing any QT prolongation.[17] In benign headaches, droperidol was superior to prochlorperazine at a dose of 2.5 mg IV or 5 mg IM.[18] A 2011 systematic review of three studies by Leong and Kelly confirm that droperidol is more effective than opioids or prochlorperazine for headaches, without an increase in adverse events.[19]

Higher doses (≥10 mg) of droperidol have been used safely for acute undifferentiated agitation in ED patients. A randomized controlled trial from 2006 found droperidol and midazolam, both starting at doses of 5 mg IV and repeated as needed up to 20 mg, equally effective for sedation of acutely agitated patients without inducing dysrhythmias or QTc changes.[20] Another randomized control trial of droperidol, 5 mg IV, found it superior to midazolam or olanzapine for agitation, without inducing dysrhythmias.[21] When combined with midazolam, droperidol (5 to10 mg IV) was even more effective in controlling severe agitation and combativeness in acute psychosis, without prolongation of QTc or cardiac adverse events.[22] Similar conclusions were found in prehospital data, where doses of droperidol up to 5 mg IV or 10 mg IM were more effective and safer than alternative medications, such as midazolam.[23] In a prospective observational study of 1,009 ED patients with acute behavioral disturbance along with close cardiac monitoring, high dose droperidol 10 to 20 mg IV (median dose, 10 mg) resulted in QT prolongation in only 1.3% (95% CI 0.7% to 2.3%) of patients without any incidence of torsades de pointes.[24] A systematic review published in 2018 confirmed the safety and efficacy of droperidol for acute psychosis-induced agitation.[25] Intramuscular doses of up to 10 mg of droperidol appear to be as safe and possibly more effective than other medications used for control of agitated patients.[22,26] There were no reports of increased cardiac or respiratory events in all of these droperidol trials. Given these trials, it can be concluded that droperidol provides a consistent effective treatment for acute agitation in the ED, thereby improving patient and provider safety.

Based on the literature, droperidol is safe for the treatment of nausea, vomiting, headaches, and agitation in the ED and prehospital environments. The FDA agrees that current literature does not support mandating a prior electrocardiogram or telemetry monitoring for doses <2.5 mg given intravenously. There should be no restrictions for use of droperidol at higher doses in the ED provided cardiac monitoring is available soon after IV administration for high risk patients: age ≥65 years, female sex, hypokalemia, or concomitant QT prolongation medications.[27,28] For agitated psychosis, because of the extensive published literature and safety, we recommend that physicians and prehospital personnel continue to use droperidol at even higher doses, starting initially at 5-10 mg IM or IV given studied doses up to 20 mg, regardless of initial monitoring capability or EKG. We also recommend that the FDA block box warning be revised to reflect the newest data regarding the safety and efficacy of droperidol for a variety of ED indications.[29]

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