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Review Article

Evidence-based review and appraisal of the use of droperidol in the emergency department

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Abstract

Droperidol is a short-acting, potent dopamine D2 antagonist that can pass through the blood–brain barrier. A black box warning was issued for droperidol by the United States Food and Drug Administration in 2001 because of a risk of development of torsades de pointes induced by QT prolongation. Many experts feel that the incidence of arrhythmia is overestimated, and low-dose droperidol is almost always used by anesthesiologists for postoperative nausea and vomiting. In this review, we used evidence-based analysis to appraise high-quality studies with a low risk of bias published after 2001 on the use of droperidol in the emergency department (ED). Droperidol appears not only efficacious but also safe to treat patients with nausea/vomiting, acute psychosis, and migraine in the ED. For these conditions, droperidol may be an option for shared decision-making.

Keywords: *Acute psychosis, Droperidol, Migraine, Nausea/Vomiting, QT prolongation*

Introduction

Droperidol is a short-acting butyrophenone compared with haloperidol. It is a potent dopamine D2 antagonist with additional effects as an α_2 adrenoceptor agonist, $5HT_3$ serotonin antagonist, H_1 histamine antagonist, γ-aminobutyric acid Type A agonist (low dose)/antagonist (high dose), anticholinesterase agent, muscarinic and nicotinic antagonist, and sodium channel blocker and has also demonstrated μ opioid receptor potentiation [1,2]. It readily crosses the blood–brain barrier with a rapid onset of action after administration and has been used as antiemetic and antipsychotic agent for over 40 years [3]. Unfortunately, severe adverse effects such as extrapyramidal syndrome, hypotension, sedation, and prolongation of the corrected QT (QTc) interval may occur with repeated and high-dose administration. A black box warning was issued for droperidol by the United States Food and Drug Administration (USFDA) on December 4, 2001, because of a risk of torsades de pointes induced by QT prolongation [3-5]. After that, the clinical use of droperidol decreased markedly [6]. Low-dose droperidol is usually prescribed by anesthesiologists to prevent postoperative nausea and vomiting [7]. The antiemetic effect of droperidol mainly originates from inhibition of the dopaminergic receptors in the chemoreceptor trigger zone [8]. However, over the past decade, increasing numbers of clinical trials have supported intravenous (IV) or intramuscular (IM) administration of droperidol for the management of several conditions in the emergency department (ED). In this review, we summarized and appraised studies of droperidol published after 2001 for the treatment of nausea/vomiting, acute psychosis, and migraine in the ED.

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Droperidol for nausea and vomiting in the emergency department

Nausea and vomiting are leading complaints of patients in the ED. Despite the diverse etiologies of these symptoms, ED physicians usually prescribe medication for relief initially. A systemic review of eight randomized controlled trials (RCTs) investigating six antiemetic drugs (metoclopramide, ondansetron, tropisetron, prochlorperazine, promethazine, and droperidol) in the adult ED setting was reported by the Cochrane library [9]. Only droperidol was observed to offer a statistically significant reduction in nausea severity 30 min after administration compared with placebo in a single trial [10] of 48 participants. The mean difference in the 100-mm visual analog scale (VAS) between droperidol and placebo was −15.80 (95% confidence interval [CI]: −26.98 to − 4.62). In this low-risk-bias study, Braude *et al.* also demonstrated significantly better efficacy for droperidol (1.25 mg IV) than

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metoclopramide (10 mg IV) or prochlorperazine (10 mg IV) in reducing nausea at 30 min [10]. Thus, a single low dose of IV droperidol may be the best therapy for patients with nausea and vomiting in the ED.

Droperidol for acute psychosis

Patients with acute psychotic episodes, especially those with agitation or violent behavior, are often brought to the ED. Tranquilizers and sedatives are usually administered immediately for the safety of patients and medical staffs, and droperidol is one of the choices. A systemic review of six RCTs which investigated the efficacy and safety of droperidol was reported by the Cochrane library [11]. One high-quality evidence-based RCT in that systemic review demonstrated that patients treated with droperidol (5 mg IV) fell asleep more rapidly at 30 min than when treated by placebo with statistical significance [12]. The number needed to treat (NNT) was around 7 (NNT = 1/absolute risk reduction [ARR] = 1/|(103/112)−(90/115)| = 7.3), which indicated a satisfactory effect. In addition, the mean time to sedation was significantly shorter than with placebo (21.3 and 67.8 min in the droperidol and placebo groups, respectively). Although clear evidence demonstrated that midazolam (median dose 5 mg IV), a rapid-onset benzodiazepine, resulted in more adequate sedation than droperidol (median dose 10 mg IV) with an NNT of 3.6 (1/|(33/74)−(13/79)|), there were no differences in other parameters including being asleep at 10 min, median time to sedation, and use of additional medication between midazolam and droperidol treatment [13]. A significantly reduced need for additional medication at 60 min was observed with droperidol compared with haloperidol, one of the most common butyrophenones in clinical use, in pooled data from 2 RCTs with low heterogeneity (relative risks, 0.37; 95% CI, 0.16–0.90; I^2 = 0.0%). However, a new RCT conducted by Calver *et al.* showed no difference in effective sedation, median time to sedation, and requirement for additional sedation between haloperidol (10 mg IM) and droperidol (10 mg IM) for patients with agitation and aggression in a psychiatric intensive care unit [13]. Heterogeneous results may occur due to multiple factors, such as the method of drug administration, varying severity of disease, and different facilities. Furthermore, although there were no clear differences between droperidol (5 mg IV) and an atypical antipsychotic olanzapine (5 mg IV) in tranquillization or being asleep at any time point, less additional medication was needed within 60 min with droperidol than olanzapine treatment [12]. In real-world practice, emergency physicians often use both antipsychotics and benzodiazepines to treat patients with acute, severely agitated states. Taylor *et al.* undertook a double-blinded RCT to compare the efficacy of a combination of midazolam (5 mg IV) and droperidol (5 mg IV), droperidol alone (5 mg IV), and olanzapine (5 mg IV) [14]. Although more patients were adequately sedated in the midazolam–droperidol group than the other groups, 10 min after the first sedative dose, the absolute difference in proportions was very small (ARR = 0.4%, NNT = 250). However, the median time to adequate sedation in the midazolam–droperidol (5 min) group was significantly shorter than the droperidol (11 min) and olanzapine (11 min) groups. These high-quality evidence with low or minimal risk of bias support the use of droperidol as a first-line or adjuvant therapy for acute psychosis in the ED.

Droperidol for migraine

Migraine is a common neurological problem in the ED. Hypersensitivity to dopamine agonists in patients with migraines indicates that dopamine may play a role in the pathophysiology of migraine [15]. Therefore, dopamine receptor antagonists have been considered a choice for the treatment of migraine. Relief of headache at 2 h was better in adults with moderate or severe migraines receiving droperidol (2.75, 5.5, and 8.25 mg IM) than placebo in one RCT [16]. When pooling the results from three different dosages, an NNT of 3.7 showed excellent efficacy for droperidol. The efficacy of droperidol (5 mg IM or 2.5 mg IV) and prochlorperazine (10 mg IM or IV), also a dopamine D2 receptor antagonist, was compared for benign headaches in ED patients in one RCT [17]. The mean decrease in 100-mm VAS scores was significantly better for droperidol treatment as early as 6 min after administration (NNT = 1/[0.814−0.669] ≒ 7). More patients receiving droperidol had at least a 50% reduction in their VAS scores than those receiving prochlorperazine at 60 min (NNT = 1/[0.902−0.686] ≒ 4.6). In this study, fewer than 30% of patients had previously diagnosed migraines in both groups. Weaver *et al.* conducted another RCT to determine the efficacy of droperidol (2.5 mg IV) and prochlorperazine (10 mg IV) for the treatment of uncomplicated headache in the ED [18]. In this study, the portion of patients with previously diagnosed migraine was not mentioned. This study was terminated early due to chronic intermittent shortages of prochlorperazine and concerns about the USFDA's "black box" warning for droperidol. Due to the above factors, the investigators failed to meet the required number of participants. Although significant, the benefits of droperidol compared with prochlorperazine were not as remarkable as in the previous study. Droperidol (2.5 mg IM) versus meperidine (1.5 mg/kg IM) for migraine in adults in ED was investigated in one RCT [19]. However, small sample sizes and differences in initial severity between the two groups caused bias of the results. In another RCT, similar effects for primary headache in the ED were observed between droperidol (5 mg IM) and olanzapine (10 mg IM) treatment [20]. The 2015 American Academy of Neurology Guideline suggested a Level B recommendation, for the use of droperidol for migraine pharmacotherapy in adults, which means the drug is probably effective based on available evidence [21].

QT prolongation and torsades de pointes: The safety issue with droperidol

The mechanism of QT prolongation induced by droperidol results from blockade of the human ether-a-go-go-related channel, which mediates repolarizing IKr current [22,23]. A prolonged QTc interval >440 ms in males or >450 ms in females is potentially harmful because it may cause the development of torsades de pointes, a life-threatening arrhythmia [24]. According to the USFDA, 52 deaths were reported between November 1997 and December 2001 after

the use of droperidol with dosages clearly above 10 mg [25]. However, in the USFDA's report, only around half of those 52 patients had QT prolongation and/or torsades de pointes, and most of them also took other medications which had risks for arrhythmia and/or death [25]. In addition, low-dose (1.25 mg or less) droperidol was considered safe because only 10 serious cardiovascular events were reported with this low dose in 127 cases of serious adverse events [26]. Therefore, many experts criticized the warning as inappropriate and felt that the USFDA had overestimated the severity [25-29]. In contrast, some experts agreed with the black box warning [30]. In spite of these disputes, the USFDA still announced that there was insufficient evidence to substantiate a lack of cardiotoxicity from low dosages of droperidol [31]. In 1997, the Committee for Proprietary Medicinal Products in the UK announced that changes of <30 ms in the QTc interval are considered unlikely to elicit the proarrhythmic potential of a drug, and some studies reported that low-dose droperidol (1.25 mg or less) prolonged the QTc interval <30 ms [32-34]. Few cases of QT prolongation, ranging from 0% to 2.7% in various studies, have been reported with dosages of 2.5–10 mg [14,16,35-37]. No cases of torsades de pointes were reported with dosages <10 mg. The risk of QT prolongation was indeed increased with dosages higher than 10 mg [38,39]. Therefore, the American Academy of Emergency Medicine Clinical Guidelines Committee has suggested that IM doses up to 10 mg seem to be safe [40]. It was impossible to calculate the NNH for arrhythmia from the above trials because most of them had no placebo controls.

Conclusion

According to the evidence, especially from low-bias, high-quality studies done after the black box warning was issued by the USFDA, droperidol appears not only effective but also safe in treating ED patients with nausea/vomiting, acute psychosis, and migraine. For such conditions, droperidol may be an option for shared decision-making. More high-quality RCTs are needed to strengthen the grade of evidence through meta-analysis.

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Conflicts of interest

There are no conflicts of interest.

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