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DROPERIDOL ANALGESIA FOR OPIOID-TOLERANT PATIENTS

John R. Richards, MD,* Irina N. Richards, MD,† Gal Ozery,* and Robert W. Derlet, MD*

*Department of Emergency Medicine, and †Department of Internal Medicine, UC Davis Medical Center, Sacramento, California
Reprint Address: John R. Richards, MD, Department of Emergency Medicine, UC Davis Medical Center, PSSB 2100, 2315 Stockton Boulevard, Sacramento, CA 95817

□ **Abstract—Background: Patients with acute and chronic pain syndromes such as migraine headache, fibromyalgia, and sickle cell disease represent a significant portion of emergency department (ED) visits. Certain patients may have tolerance to opioid analgesics and often require large doses and prolonged time in the ED to achieve satisfactory pain mitigation. Droperidol is a unique drug that has been successfully used not only as an analgesic adjuvant for the past 30 years, but also for treatment of nausea/vomiting, psychosis, agitation, sedation, and vertigo. Objectives: In this review, we examine the evidence supporting the use of droperidol for analgesia, adverse side effects, and controversial United States (US) Food and Drug Administration (FDA) black box warning. Discussion: Droperidol has myriad pharmacologic properties that may explain its efficacy as an analgesic, including: dopamine D2 antagonist, dose-dependent GABA agonist/antagonist, $\alpha 2$ adrenoreceptor agonist, serotonin antagonist, histamine antagonist, muscarinic and nicotinic cholinergic antagonist, anticholinesterase activity, sodium channel blockade similar to lidocaine, and μ opiate receptor potentiation. Conclusion: Droperidol is an important adjuvant for patients who are tolerant to opioid analgesics. The FDA black box warning does not apply to doses below 2.5 mg.** © **2011 Elsevier Inc.**

□ **Keywords—droperidol; analgesia; emergency department; opioid tolerance; chronic pain**

INTRODUCTION

Patients with acute and chronic non-malignant pain represent a significant proportion of those seeking care at emergency departments (EDs) (1–3). A subset of these patients have opioid tolerance from prolonged use of prescription and non-prescription opioid analgesics, or have genetic polymorphism (4,5). They may require multiple and large doses of opioids with extended periods of time in the ED to achieve acceptable analgesia. This results in need for close monitoring for respiratory depression, which in turn may lead to worsening crowding as ED beds become occupied for lengthy periods and nursing resources are stretched (6,7). Chronic pain patients may insist on specific opioid analgesic regimens, often via an intravenous (i.v.) or intramuscular (i.m.) route. This often places clinicians in a difficult position if they do not acquiesce (8). Furthermore, it may be difficult to distinguish between patients who have bona fide exacerbation of chronic pain and malingerers (9). This problem also extends to patients addicted to non-prescribed opioid analgesics and illicit drugs such as heroin (10). Emergency physicians strive to mitigate their patients' pain as quickly, safely, and ethically as possible. Use of large doses of opioid analgesics in patients who are tolerant or may be malingering should be avoided whenever possible (11). Furthermore, parenteral opioid use in a subset of chronic pain patients may enhance pain sensitivity (12). The use of alternative medications, if indicated, should be considered in this subgroup. Implementation of a non-opioid protocol at one university ED effectively reduced the number of visits by this patient population and enabled some to be weaned off opioid analgesics entirely (13). One of the alternative

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drugs used in the aforementioned study, droperidol (Inapsine®; Akorn Inc., Lake Forest, IL), has several unique pharmacologic properties and shall be discussed further as a potential adjuvant in this clinical setting.

DISCUSSION

Pathophysiology and Pharmacology

The process of nociception is complex and involves distinct nerve pathways from the periphery to the central nervous system (CNS), as well as neurotransmitters, receptors, inflammatory modulating substances, and genetic factors (14–18). Pain is essential for human survival, but chronic or sustained pain has been shown to result in alteration of gene expression within the CNS, development of dysphoria, and diminished quality of life (14). Dopamine in the CNS has an important role in pain modulation (15–17). Furthermore, chronic opioid use and pain syndromes such as fibromyalgia and migraine headache have been shown in both animal and human studies to result in significant alteration in CNS dopamine receptor regulation, gene expression, and binding properties (18–24).

Droperidol is a high-potency, rapid-acting butyrophenone, similar to haloperidol, that has been used worldwide since its discovery in 1961, and in the United States since approval by the Food and Drug Administration (FDA) in 1970 (25). Droperidol has several pharmacologic properties that may account for its protean clinical applications, such as for treatment of emesis, vertigo, psychosis, agitation, anxiety, and analgesia (26). Droperidol is primarily an antagonist of dopamine D2 receptors in the CNS, specifically the subcortical, midbrain, and brainstem reticular formation. It is also an $\alpha 2$ agonist, which may account for some of the observed analgesic effects (25–28). Droperidol is an antagonist of CNS histamine and serotonin receptors (25–28). The antihistaminic property of droperidol may enhance its sedating effect (29). Droperidol has also been shown to block vasoconstriction by several vasoactive agents (30). Droperidol has been shown to have anticholinesterase activity as well as mild antagonism of muscarinic acetylcholine receptors (31,32). This may explain its amnestic and behavioral modification effects.

CNS dopaminergic systems act as negative modulators of opiate analgesia, whereas serotonergic and cholinergic systems act positively (14,33). In one study, dopaminergic receptor stimulation, inhibition of serotonin synthesis, and blockade of muscarinic receptors led to inhibition of morphine analgesia (33). Conversely, dopaminergic receptor antagonism or increase in serotonergic or cholinergic activity resulted in the enhancement of morphine analgesia in the same study. Another potential explanation for its observed analgesic potentiation is that droperidol inhibits CNS neuronal nicotinic acetylcholine receptors, which have been implicated in the mechanism of action of all intravenous and gaseous general anesthetics (34,35). Droperidol also has affinity for γ-aminobutyric acid type A (GABA-A) receptors, which seems to be dose-dependent. Low-dose droperidol causes antagonism, and higher doses result in agonism (35). This GABA-A effect may explain why certain patients achieve a calm, indifferent state and others experience dysphoria and anxiety after receiving droperidol. However, unlike benzodiazepines, droperidol does not cause respiratory depression.

Another mechanism of analgesia is attenuation of pain at the level of the spinal cord. Droperidol has structural similarities to lidocaine and a reversible local anesthetic effect (36). Both drugs are comprised of a lipophilic ring system on one end of the molecule connected by an aliphatic chain with a tertiary amine on the other end (Figure 1). The intermediate aliphatic chain contains an ester bond in droperidol and an amide bond in lidocaine. Dorsal horn neurons located in the spinal cord process and transmit nociceptive information (14). Olschewski and colleagues demonstrated that droperidol suppresses voltage-gated sodium conductance in spinal dorsal horn neurons, with fast sodium channels twice as sensitive to droperidol as slow channels (37). This effect differs from local anesthetics and tetrodotoxin, which equipotently suppress fast and slow sodium current. This same research group reported that droperidol also blocks the delayed rectifier potassium channel of spinal sensory neurons, which further enhances its anesthetic effect (38). Before these studies, Radke and associates demonstrated that droperidol does not block sodium channels in the CNS (39).

Droperidol may directly modulate CNS opiate receptors. It was first reported in 1979 that droperidol potentiated the effects of leucine-enkephalin, an endogenous opioid (40). Vargas and colleagues demonstrated in two studies that droperidol and haloperidol resulted in release of endorphins in an animal model (41,42). Zhu and co-workers have studied the effect of droperidol on CNS μ (mu) opiate receptors, monoamine content, and preproenkephalin mRNA expression in an animal model. This research group reported that μ receptor binding and availability during electroacupuncture was further enhanced by droperidol administration, while confirming its dopaminergic and serotoninergic effects (43,44). Possible explanations for the effect observed for μ and perhaps other opioid receptors is that droperidol results in increased expression or decreased degradation of opiate receptor mRNA (45). Dopamine has an inhibitory effect on the enkephalinergic system, and droperidol antagonism may diminish this inhibition. A summary of

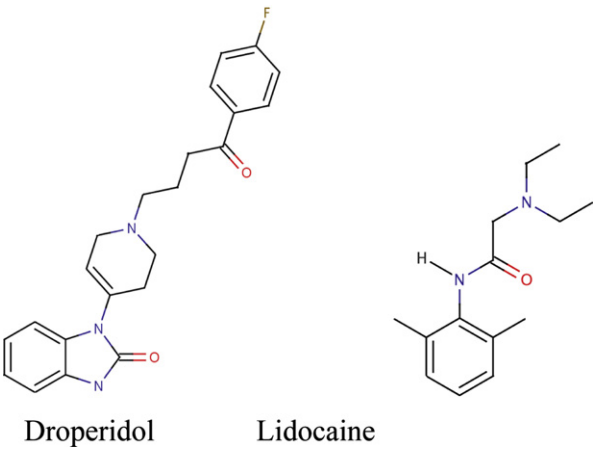

Figure 1. Chemical structure of droperidol and lidocaine.

the putative pharmacologic effects of droperidol to explain its analgesic properties is shown in Table 1, and potential targets in the CNS in Figure 2.

Clinical Evidence

Admiraal and associates first described the successful use of droperidol for chronic pain patients in 1971 (46,47). There are several human studies that have specifically addressed the analgesic effect of droperidol in the ED for treatment of headache. Wang and colleagues first studied the use of i.v. droperidol for this indication and achieved a success rate of 88% of 25 patients with status migrainosus and 100% of those with refractory migraine (48). Miner et al. conducted a prospective, single-blind comparison of i.m. or i.v. droperidol and prochlorperazine in the treatment of benign headaches and reported that 61% of the 82 study participants receiving droperidol and 44% of the 86 receiving prochlorperazine achieved significant pain relief at 30 min (49). Another prospective study of both drugs had similar results (50). Richman and colleagues reported symptomatic relief in 81% of patients with migraine headache after receiving droperidol (51). This same research group then conducted a prospective comparison between droperidol and meperidine and reported similar outcomes between the two drugs (52). Silberstein et al. demonstrated that droperidol was effective for migraine headache treatment when compared to placebo (53). Most recently, Hill and associates compared droperidol to the second-generation neuroleptic olanzapine and found both had similar analgesic properties (54). Droperidol has also been reported effective for termination of organic, non-migraine headache. Mendizabal described 2 patients with resolution of severe headache after receiving droperidol in the ED who were later diagnosed with meningitis and a brain tumor (55).

Anesthesiologists have used droperidol extensively for postoperative nausea and vomiting since its advent and

Table 1. Droperidol Analgesia: Putative Mechanisms of Action within the CNS

Dopamine D2 antagonist
GABA agonist/antagonist (dose-dependent)
α2 adrenoreceptor agonist
Serotonin antagonist
Histamine antagonist
Muscarinic and nicotinic cholinergic antagonist
Anticholinesterase activity
Sodium channel blockade, local anesthetic effect
μ (mu) opiate receptor potentiation

have reported its unique analgesic properties in many communications. The concept of neuroleptanalgesia was described four decades ago with the combination of droperidol with fentanyl (Innovar®, Janssen Pharmaceuticals, New Brunswick NJ) for procedural sedation (56). The addition of droperidol enabled clinicians to reduce the amount of fentanyl given and the risk of respiratory depression, while enhancing amnesia. This opioid-sparing effect has been described with droperidol use in patient-controlled analgesia (PCA). Sharma and Davies reported improved analgesia and patient satisfaction with combination morphine and droperidol vs. morphine alone in a prospective study of post-hysterectomy PCA patients (57). This outcome in post-hysterectomy patients was also reported by Lo and co-workers (58). Freedman and associates had similar results in PCA patients after orthopedic surgery (59). Yamamoto et al. described decreased morphine use and improved analgesia in patients who underwent rotator cuff repair and received droperidol preoperatively vs. postoperatively (60). Dresner and colleagues compared the addition of droperidol vs. ondansetron to morphine PCA and reported that the ondansetron subgroup utilized more morphine and was a more expensive regimen overall (61).

The use of droperidol in epidural anesthesia is well-documented. Bach and associates first described enhanced analgesia with epidural droperidol in chronic pain patients who had developed tolerance to epidural opioids (62). Epidural droperidol has also been shown to enhance analgesia for postoperative pain (63,64). Naji and coworkers reported improved analgesia and decreased morphine usage in patients who underwent hip replacement surgery (65). This same research group later compared the addition of droperidol to epidural sufentanil in patients who underwent hip and knee arthroplasty and found that droperidol enhanced analgesia and reduced the side effects of nausea, emesis, and pruritis (66). This added benefit of droperidol was also reported by Kotake et al. in their postoperative comparison of epidural fentanyl with droperidol or butorphanol (67). The authors described improved analgesia and less nausea and vomiting in the subgroup receiving droperidol. Similar outcomes were reported by Ben-David and colleagues in their comparison of epidural fentanyl with

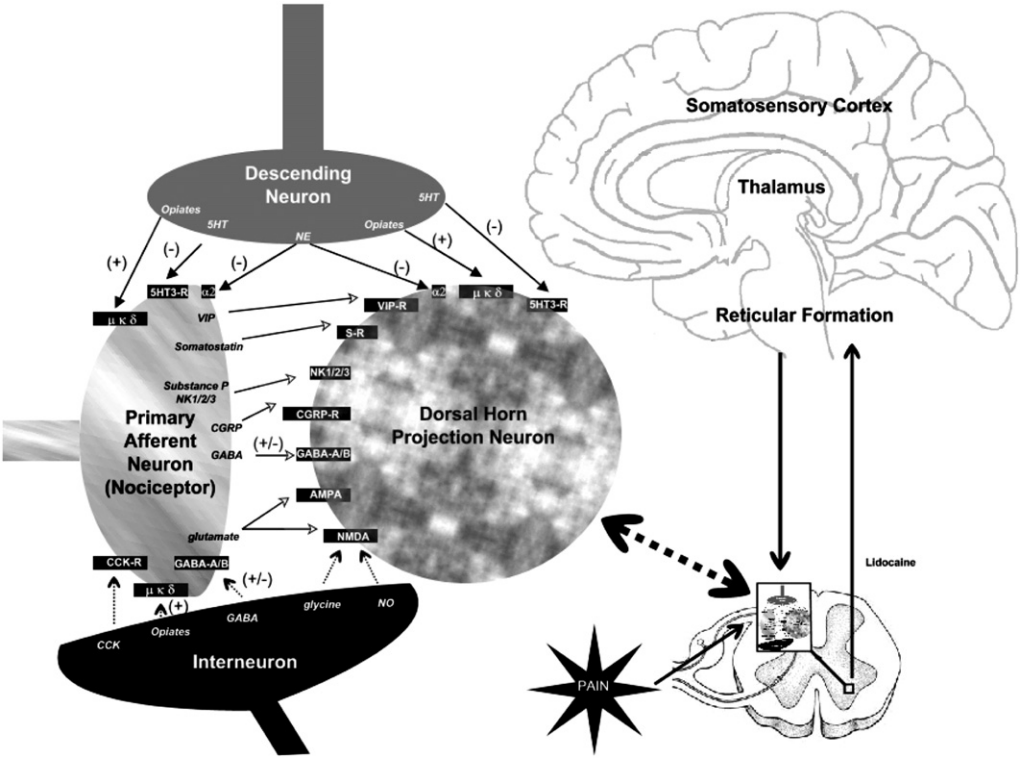

Figure 2. Droperidol modulation of spinal cord pain transmission. Dorsal horn projection neuron receptors: Serotonin (5HT3-R), endorphins ($\mu\ \kappa\ \delta$), alpha 2 adrenoreceptor ($\alpha 2$), vasopressin inhibitory protein (VIP-R), somatostatin (S-R), substance P (NK1/2/3), calcitonin G-related peptide (CGRP-R), γ-aminobutyric acid (GABA-A/B), alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), N-methyl-d-aspartate (NMDA). Cholecystokinin receptors (CCK-R) are located on the primary afferent neuron terminal. Other neurotransmitters include nitric oxide (NO) and norepinephrine (NE). Droperidol may also have a local anesthetic effect similar to lidocaine within the spinal cord. (+) = agonist; (−) = antagonist; (+/−) = mixed effect.

droperidol or nalbuphine (68). The addition of droperidol to epidural tramadol, a non-opioid analgesic with μ receptor agonism and noradrenergic and serotoninergic effects, also has been shown in two prospective, randomized studies to enhance its analgesic properties (69,70). Finally, the combination fentanyl and droperidol has been used for patients with acute myocardial infarction to mitigate pain and anxiety (71,72). To date, no further studies with droperidol have been performed in patients with coronary heart disease.

Clinical Use

For patients with acute exacerbation of chronic pain syndromes or who are tolerant of opioid analgesics, droperidol may be used either i.v. or i.m. (73). Typical starting dosage ranges from 0.625 to 2.5 mg for this indication; higher doses are reserved for patients with acute agitation or psychosis (74,75). This dosage range has also been shown to be effective for nausea, vomiting, vertigo, and light sedation (76–80). Droperidol administration may be repeated, but this is usually not necessary. Onset of action is biphasic, with initial effect observed 3–10 min after i.v. and i.m. administration and peak response at 30 min (81). Elimination half-life in adults is 134 $\pm$ 13 min and may be increased in geriatric patients. In children, it is 101.5 $\pm$ 26.4 min. There is extensive protein binding after administration. Droperidol crosses the blood-brain barrier and is distributed into cerebrospinal fluid. There is slow transfer of the drug across the placenta, and no fetal harm has been reported with use of droperidol in pregnancy (category C). Metabolism is hepatic with inactive metabolites excreted via urine and feces. In 1970 the FDA approved droperidol for nausea, vomiting, anxiety, and sedation. Droperidol is currently FDA-approved for only nausea and vomiting; all other uses are considered "off-label," including doses < 2.5 mg.

Adverse Effects

Akathisia and dystonia are adverse effects associated with neuroleptics and many antiemetics. It is the most common adverse effect with droperidol, and symptoms can range from mild to severe (82–85). Akathisia is believed to be precipitated by CNS imbalance of dopaminergic inhibition of cholinergic pathways, but serotoninergic and endogenous opioid systems may also be involved (86). Akathisia is rarely encountered in acutely agitated

or psychotic patients treated with dopamine antagonists, as there is excess CNS dopamine that cannot be overcome at normal dosage range. Treatment with anticholinergics such as benztropine or diphenhydramine is usually effective at terminating akathisia. More severe akathisia and dystonia may also require beta-blockers and benzodiazepines (86). Sedation is another adverse effect of droperidol and is likely a result of its aforementioned anticholinergic and mixed GABAergic properties (87). This may actually be advantageous when droperidol is used for procedural sedation or agitation. Patients receiving droperidol should be warned against driving or operating heavy machinery for 24 h (88).

Pretreatment with diphenhydramine 25–50 mg i.v. or i.m. to preclude akathisia in patients with prior history of dystonia to antiemetics may be prudent. To date, no studies have been published regarding this issue for droperidol, but several exist for other related drugs. Vinson and Drotts reported a 22% reduction in the incidence of akathisia with diphenhydramine pretreatment for patients receiving i.v. prochlorperazine (89). Friedman et al. concluded that pretreatment with diphenhydramine reduced akathisia in patients receiving higher-than-normal doses of metoclopramide (90). Slow infusion of prochlorperazine does not seem to affect development of akathisia (91,92).

Droperidol is one of many commonly used drugs that prolong the QT interval (93,94). In 2001 the FDA placed a black box warning on the use of droperidol for doses > 2.5 mg (95). This warning has caused considerable controversy among anesthesiologists and emergency physicians, as many believe it is unwarranted; however, a majority of clinicians have decided to discontinue using droperidol for any indication as a result of the warning (95). A screening electrocardiogram to measure the QT interval before administration of droperidol is recommended but not required for doses ≤ 2.5 mg. In 2003 the FDA Anesthetic & Life Support Drugs Advisory Committee stated, "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." (96). Despite this warning, droperidol has an excellent safety profile (97–101). In 2000, just before the black box warning, approximately 25 million unit doses of generic droperidol were sold worldwide (77). Only 10 adverse cardiac events were reported to the FDA for patients receiving 1.25 mg of droperidol or less, and all had confounding factors making it impossible to determine causation (97). In a large retrospective study, Nuttall and associates reviewed 16,791 patients exposed to low-dose droperidol, and none experienced torsade de pointes or other dysrhythmia due to QT interval prolongation (102).

CONCLUSION

Patients with acute and chronic pain who are tolerant to opioid analgesics may respond to droperidol in a range of 0.625–2.5 mg i.v. or i.m. Pretreatment with diphenhydramine may mitigate or prevent akathisia. Screening for QT interval prolongation before administration of droperidol, and cardiac monitoring for 2 to 3 h thereafter is prudent but not essential, according to current FDA doctrine. The FDA black box warning does not apply to doses below 2.5 mg. Patients should be warned about sedation and instructed not to drive or operate heavy machinery for 24 h. We believe this regimen represents a progressive, alternative approach to treating patients who fail to respond to opioid analgesics in large and frequent doses while avoiding complications such as respiratory depression, prolonged time in the ED, or propagating addictive behavior.

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ARTICLE SUMMARY

1. Why is this topic important?

Patients who are tolerant to opioid analgesics are difficult to treat in the emergency department (ED) and may require large, escalating doses of opioids to achieve satisfactory pain control. Droperidol represents an alternative to opioid analgesics for this subset of patients.

2. What does this review attempt to show?

This is an extensive review of the unique pharmacologic properties of droperidol and its clinical use as an analgesic.

3. What are the key findings?

Droperidol has many properties that may explain its analgesic effect, and it has been shown in several clinical studies to have efficacy as an adjuvant to opioid analgesics.

4. How is patient care impacted?

Opioid-tolerant patients may achieve significant analgesia with droperidol in lieu of escalating doses of opioids. This may lead to shorter length of stay in the ED and fewer complications such as respiratory depression.