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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