Opioids, Sedatives, and Sleep Hypoventilation

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KEYWORDS

• Opioids • Hypoventilation • Sedatives • Sleep-disordered breathing • Sleep apnea
• Benzodiazepines • Ventilatory response

KEY POINTS

- The emphasis on effectively treating chronic pain syndromes has led to a large increase in the number of patients on opioid medications chronically.
- An increasingly recognized adverse effect of long-term opioid usage is sleep-related respiratory disorders, including sleep hypoventilation and sleep apnea.
- Sleep-related hypoventilation secondary to opioid use is associated with hypercapnia caused by a blunted hypercapnic ventilatory response, decreased respiratory drive, and possibly reduction in upper airway muscle tone.
- The combination of opioids and sedatives, individually working on different receptors, could synergistically cause severe respiratory depression during sleep.
- Treatment of opioid-induced sleep hypoventilation includes taper of dosage or withdrawal of the medication if possible, or use of noninvasive positive pressure ventilation devices to support breathing during sleep.

INTRODUCTION

The treatment of pain, both acute and chronic, is justifiably becoming more important. The presence of chronic pain is associated with decreased quality of life, and effective therapy with improvement.[1] Pain adversely effects both physical and mental health and has become a public health concern. Pain is considered a vital sign in medical clinics across the country. Beginning in 1997, the American Academy of Pain Medicine in conjunction with the American Pain Society issued a consensus supporting the use of opioids for the treatment of chronic pain.[2] Even before this statement was released, opioid usage was increasing, with a further increase in methadone and oxycodone usage by 824% and 660% from 1997 to 2003, respectively.[3] The escalation in opioid prescriptions is a result of increased awareness by health care providers to treat chronic pain and awareness by patients to seek treatment.

Opioids are effective and widely prescribed analgesics, but their use is limited by several problematic side effects. One of the more concerning and recognized adverse effects, to which tolerance does not develop with long-term treatment, is respiratory depression during sleep. This depression can manifest in a variety of ways, being in the category of sleep-related breathing disorders. There is a paucity of data on treatment options and the effectiveness of these options for patients with sleep-related breathing disorders including sleep hypoventilation associated with chronic opioid use. Furthermore, there is no clear consensus on how best to manage opioid-induced sleep-related breathing disorders, apart from using the lowest effective opioid dose. The adverse effects of chronic opioid use on respiration during sleep, specifically hypoventilation,

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and potential additive consequences when combined with sedatives, are reviewed here along with potential treatment options.

MECHANISMS OF OPIOID-INDUCED SLEEP HYPOVENTILATION

Opioid Receptors

Opioid receptors are a family of G-protein–coupled receptors (GPCRs). Ligand binding of opioid receptors activates inhibitory intracellular pathways leading to a reduction in neuronal excitability. Opioid receptors are widespread throughout the body and mediate multiple physiologic responses including pain, respiratory control, stress, appetite, and thermoregulation. There are 4 types of opioid receptors: delta (DOP) receptor, mu (MOP) receptor, kappa (KOP) receptor, and nociceptin/orphanin FQ peptide (NOP) receptor. Each receptor is associated with one or more endogenous ligands, including endorphins, enkephalins, dynorphins, and nociceptin/orphanin. Opioids induce respiratory depression chiefly through their actions on mu and kappa receptors, both of which are located centrally and peripherally. Opioids treat pain through these receptors as well.

Respiratory Rhythm Generation

Experimental studies in neonatal rats have improved understanding of how respiration is controlled. Respiratory rhythm generation occurs in the ventrolateral medullary portion of the rat brainstem in 2 distinct complexes: the pre-Bötzinger complex (pre-BotC) and the retrotrapezoid nucleus/parafacial respiratory group (RTN/pFRG), which are coupled and generate normal respiration rhythm.[4–6] The pre-BotC and RTN/pFRG together control respiration with the hypothesis that intrinsic pacemaker cells within these structures modulate respiratory rhythm. Respiratory rhythm in these complexes persists en bloc and in slices even after attenuation of postsynaptic inhibition, supporting the hypothesis that intrinsic rhythmical pacemaker neurons located in these complexes are driving the respiratory rhythm.[5] These findings have not been replicated in human studies.

Opioid Receptors and Respiratory Rhythm Control

Opioid receptors are found preferentially in the inspiratory generating pre-BotC.[5] A study by Mellen and colleagues[7] showed that when the potent mu-opioid agonist D-Ala2-MePhe4-Glycol5 Enkephalin (DAMGO) was added to the rat brainstem containing only pre-BotC, respiratory rhythm slowed. When DAMGO was added to the rat brainstem containing both pre-BotC and RTN/pFRG, the respiratory pattern became irregular with subthreshold action potentials still occurring regularly from the pre-BotC, but the action potentials were not transmitted. This effect is likened to the pathophysiology of Mobitz type II second-degree heart block occurring in control of respiration and supports the hypothesis that the RTN/pFRG also has inspiratory controlling capabilities in the absence of pre-BotC function.[7]

In animal studies, the pre-BotC seems to be the dominant site for inspiration and contains the neurokinin-1 receptor (NK1R) and mu-opioid receptor.[8] The anatomic region corresponding with the pre-BotC is identified by NK1R expression and in vitro electrophysiology. In rhythmically active brainstem section in vitro, NK1R expressing pre-BotC neurons are selectively inhibited by opioids.[9] Continuous local unilateral application of a mu-opioid receptor agonist DAMGO or fentanyl into the pre-BotC in adult rats caused sustained slowing of respiratory rate and increased respiratory rate variability (ataxic breathing). At sufficient concentrations of mu-opioid agonist, complete cessation of breathing was seen, as manifested by complete cessation of diaphragmatic muscle activity. Infusion of a mu-opioid agonist caused a state-dependent respiratory rate depression that is most profound in non–rapid eye movement sleep and during anesthesia.[10] These changes were fully reversed by the mu-opioid receptor antagonist naloxone.

HYPERCAPNIC AND HYPOXIC VENTILATORY RESPONSE

Metabolic control of breathing is largely determined by interactions between central and peripheral chemoreceptors. Central chemoreceptors are located in the brainstem; specifically the nucleus tractus solitaries, dorsal respiratory group, medullary raphe, and the aforementioned pre-BotC and RTN/pFRC group. Central chemoreceptors are stimulated by $Paco_2$/hydrogen ion concentration $[H^+]$ in their environment.[11] The degree of ventilatory stimulation for a given level of $Paco_2$ greater than eupnea is known as the hypercapnic ventilatory response (HCVR). HCVR greater than eupnea is most commonly measured by rebreathing techniques while awake. The slope of the hypercapnic ventilatory response is determined by the change in ventilation for an increase in $Paco_2$ of 1 mm Hg. The slope of this response is mediated by the interactions of both central and peripheral chemoreceptors.[12]