Drug-Induced Sleep-Disordered Breathing and Ventilatory Impairment

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KEYWORDS

• Sleep apnea • Hypoventilation • Opiates • Benzodiazepines • Growth hormone • Anabolic steroids • Baclofen

KEY POINTS

- To assess the risk and severity for drug-induced sleep-disordered breathing (SDB), it is important to consider patients' clinical data and comorbidities.
- Opiates can induce clinically relevant central and obstructive SDB with a very typical breathing pattern.
- Benzodiazepines can induce obstructive and reduce central SDB. The negative effects may be limited in most patients but older age, comorbidities, and known severe sleep apnea are strong contraindications as long as sleep apnea is untreated.
- Additional drug classes with a potential for respiratory impairment during sleep include growth hormone, phosphodiesterase inhibitors, baclofen, and sodium oxybate.
- When sleep apnea is already known and treated, such drug classes can be used with caution.

INTRODUCTION

The interaction between certain drug classes and SDB is of clinical relevance for sleep medicine. Specific patient populations with acute and chronic pain, chronic insomnia, or hormone replacement treatment may face the induction of SDB. In more severe cases, nocturnal hypoventilation and respiratory failure have been reported as adverse effects of commonly used medications. Abuse of pain killers or anabolic steroids constitute another problem that may compromise adequate breathing during sleep. Current classification of sleep disorders characterizes the different subtypes of drug-induced SDB.[1] This article summarizes the current knowledge and suggests problem-solving strategies in certain clinical situations.

Data on the effect size of drug-induced SDB are conflicting. A recent Cochrane analysis studied the effects of 10 different drugs potentially affecting respiration during sleep.[2] A total of 293 subjects with verified sleep apnea, often of mild to moderate degree, from 14 randomized controlled studies were included in the analysis. Drugs investigated were the opiate remifentanil and benzodiazepine-receptor agonists, such as eszopiclone, zolpidem, brotizolam, flurazepam, nitrazepam, ramelteon, and sodium oxybate, used in the treatment of narcolepsy. Within-group comparisons showed only mild deteriorations in overnight oxygenation and apneic events; no systematic increases in the apnea-hypopnea index (AHI) or the Oswestry disability index were observed. Some studies even showed beneficial effects on the AHI (eszopiclone and sodium oxybate). The investigators concluded that there was no current evidence for a systematic deterioration of SDB by the investigated substances.

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In sharp contrast, data from large pharmacovigilance databases using a case-control design suggest that benzodiazepines (odds ratio [OR] 2.6), opium alkaloids (OR 2.1), sodium oxybate (OR 64.3), and other psychotropic agents may significantly increase the risk for sleep-disordered breathing classified as a severe adverse drug reaction.[3] These studies clearly demonstrate that the population of patients at risk may vary significantly between the randomized controlled trial (RCT) settings and clinical reality. Safe and beneficial administration of those drugs depends greatly on a careful patient selection and treatment follow-up.

OPIATES

Opiate treatment is accompanied by the well-known side effect of respiratory depression, which becomes most clinically relevant during sleep.[4] Both conditions have synergistic effects on breathing by reducing respiratory rate and decreasing tonic respiratory drive. Animal experiments have elegantly shown the dose-response relationship between pharmacologic mu-receptor stimulation by opiates and 2 major effects on breathing during sleep[5]:

1. Reduction of upper airway muscle tone
2. Reduction of respiratory rate and irregular breathing (atactic breathing).

These animal studies showed that the effect of opiates is generated by neurokinin-1 receptor-stimulation of pre-Bötzinger complex respiratory neurons and that the pharmacologic blockage of those receptors was able to reverse the opiate-induced respiratory depression.[5]

In human sleep studies, both effects have been known for longer time and a dose-response relationship between opiate use and obstructive sleep apnea (OSA) has been established.[4,6–8] In addition, frequent central sleep apneas and irregular breathing have been identified in patients using opiate treatment.[9–11] A typical opiate-induced respiratory pattern during sleep is illustrated in **Fig. 1**. The combination of the previously mentioned effects (1) and (2) may lead to significant sleep-related hypoventilation. This risk is particularly present in patients with risk factors for hypoventilation during sleep, including comorbid obesity, respiratory disease (eg, chronic obstructive pulmonary disease [COPD]), neuromuscular disease, preexisting severe obstructive OSA, or in the elderly (**Table 1**).

Given the knowledge previously summarized, several clinical scenarios need to be addressed. First, patients with chronic pain have often typical risk factors for SDB, such as older age or obesity. This increases the likelihood of undiagnosed preexisting sleep apnea in pain patients receiving opiate treatment. Indeed, a strong association has been recognized between SDB, obesity, and pain.[12] One potential mechanism may be linked to nocturnal hypoxia as an enhancer of pain on awakening[12] and pain was reported to be improved after alleviation of nocturnal hypoxia by

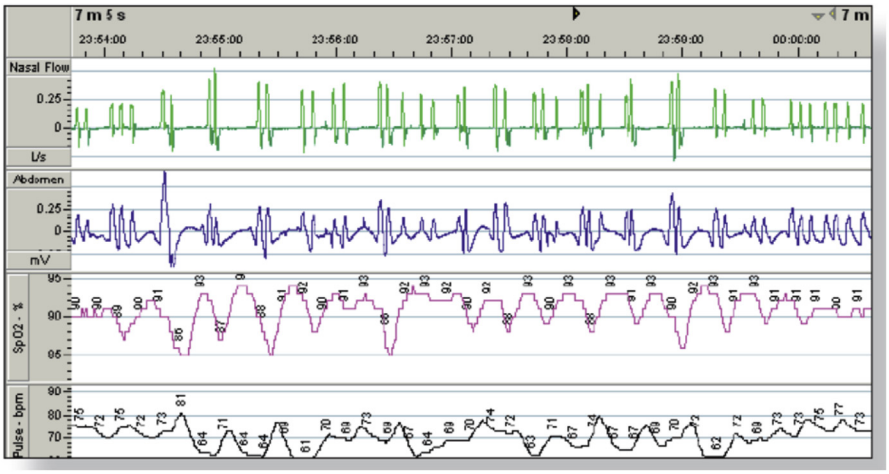

Fig. 1. Opiate-induced central sleep apnea in a 32-year-old man participating in a methadone program. A repetitive lack of flow and effort occurs in the nasal flow and the abdominal effort signals, which indicates repetitive central apneas of short duration. Mild oxygen desaturations can be detected in the oxygen saturation signal (SpO_2). Highly characteristic for opiate-induced central sleep apnea are the high variability of apnea length and the irregularity of the respiratory effort.