Suboxone (Buprenorphine/Naloxone) and Sleep-Disordered Breathing, or

Look Out for that Low Ceiling!

Robert J. Farney MD
Sleep Medicine Division, Intermountain Healthcare
Salt Lake City, Utah

Opioid medications are the mainstay of therapy for severe acute pain and for pain associated with malignancy. They have also become widely used for chronic non-malignant pain. Although the potential for serious adverse effects caused by opiates on the respiratory system (including the possibility of unintentional death) has been known for centuries, the association of sleep disordered breathing, chronic opioid exposure and increased mortality rate, has only recently been recognized.[1-4]

The mortality rates associated with the use of non-illicit opioids have increased in parallel with the unprecedented escalation of opioid prescriptions. Between 1997 and 2006, the retail distribution of oxycodone increased 832%, hydrocodone 344%, morphine 296%, fentanyl 579% and methadone 1,276%. The link between increased mortality rates and prescriptions for opioids is underscored by data reported from the state of Utah.[5, 6] In 2005, Utah had the highest rate in the nation of reported non-medical use of pain relievers and opioid related deaths.
Comparing the periods of 1991-1998 with 1999-2003, the mortality rate (number of cases/100,000) due to non-illicit use of opioids, increased 200% from 1.47 to 4.4. The mortality rate increased 261% for females compared to 163% in males (1.08 to 3.90 and 1.86 to 4.90 respectively). In the non-obese (BMI < 25 kg/m²), the mortality rate increased 208% (1.17 to 3.61) compared to 135% (6.06 to 14.25) in the obese (BMI ≥ 30 kg/m²). The mortality rates for methadone and oxycodone increased from 2.3 to 32.7 (1,358%) and from 3.9 to 16.5 (1,676%) respectively.

Although the underlying mechanisms responsible for unexpected death associated with opioids are unclear, respiratory disturbances are likely involved. Chronic opioid use reduces respiratory drive, destabilizes pacemaker neurons that generate a regular breathing pattern during non-rapid eye movement sleep, and simultaneously disables the normal protective arousal responses to hypoxemia during sleep with potentially fatal consequences. Accordingly, patients using chronic opioids may be at risk for exceptionally complex and potentially lethal disorders of breathing during sleep including central and obstructive apneas/hypopneas, ataxic breathing and hypoxemia. In addition, cardiac arrhythmias secondary to direct effects or exacerbated by sleep apnea and hypoxemia could also be responsible. Previous studies have revealed that methadone in particular can significantly prolong the Q-T interval on the electrocardiogram, a known risk factor for syncope and potentially lethal arrhythmias such as torsade de pointes.[7]
Buprenorphine is a partial \( \mu \)-agonist semisynthetic opioid (25-50 times more potent than morphine) with very high receptor affinity (1000 times greater than morphine) and long dissociation half-life [8, 9]. Although it maintains an analgesic dose response across all levels, it appears to have a flat or U-shaped biologic response on respiratory suppression such that with increasing doses, it has a lower maximum or ceiling effect. In both animal and human studies, for example, the ventilatory response to hypercapnia does not continually decrease with progressively greater doses while the analgesic effect is maintained [10-15]. When compared to methadone, the effects of buprenorphine on cardiac repolarization are negligible which suggests that its potential for inducing fatal arrhythmias is minimal. [16, 17] Consequently, it is regarded as a safer opioid compared to methadone and has become widely used for therapy of opioid dependency and chronic pain control since it was patented in 1969 and was approved for marketing in the United States in 1981. Based upon the most extensive worldwide experience in France, where general practitioners have been permitted to prescribe buprenorphine since 1996, the estimated yearly death rate (1994-1998) for methadone was at least three fold greater than the death rate related to buprenorphine [18, 19].

Prompted by our own anecdotal observations of typical opioid breathing patterns occurring in patients treated with buprenorphine/naloxone (Suboxone)
and in whom there did not seem to be other risk factors, we implemented a care process model in which all patients admitted for detoxification therapy using buprenorphine are first evaluated by sleep medicine and then undergo standard polysomnography prior to discharge.[20] Sleep testing is performed after the patients have abstained from using opioids for 12-24 hours and buprenorphine has been introduced during the stabilization phase. We reported the data from 70 consecutive patients, the majority of whom were young (mean age ± SD = 31.8 ± 12.3 years), non-obese (mean BMI ± SD = 24.9 ± 5.9 kg/m²) and female (60%).

The respiratory effects of opioids were manifest in three semi-autonomous domains: fundamental breathing pattern (ataxia versus regular breathing rhythm), breathing interruptions (apneas and hypopneas) and gas exchange (hypoxemia).

Based upon the apnea/hypopnea index (AHI), at least mild sleep disordered breathing (AHI ≥ 5/hr) was present in 63% of the group. Moderate (AHI ≥15 to < 30/hr) and severe sleep apnea (AHI ≥ 30/hr) was present in 16% and 17% respectively. Hypoxemia, defined as an SpO2 of < 90% for ≥ 10% of sleep time, was present in 27 patients (38.6%). The presence and severity of breathing disturbances was not predicted by concomitant use of benzodiazepines or neuroleptics, buprenorphine dose or by standard risk factors for OSA.

Compared to methadone, use of buprenorphine may be less likely to result in fatal overdoses at least based upon the limited clinical studies so far; however, there have been no systematic studies of the effects of buprenorphine on
respiration during sleep until now. Our observations should raise concern about
the potential for adverse and possibly lethal respiratory consequences during sleep
using ordinary doses of buprenorphine.
REFERENCES:


