Opioid-Induced Sleep Apnea: Is It a Real Problem?

Article *in* Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine · October 2012

Impact Factor: 3.05 · DOI: 10.5664/jcsm.2162 · Source: PubMed

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http://dx.doi.org/10.5664/jcsm.2162

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Commentary on Ramar et al. Adaptive servoventilation in patients with central or complex sleep apnea related to chronic opioid use and congestive heart failure. J Clin Sleep Med 2012;8:569-576.

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In 1997 the American Academy of Pain Medicine and the American Pain Society stated that "it is now accepted…that respiratory depression induced by opioids tends to be a short lived phenomenon, generally occurs only in opioid-naïve patients and is antagonized by pain. Therefore, withholding the appropriate use of opioids from a patient who is experiencing pain on the basis of respiratory concerns is unwarranted."[1] In addition, Papaleontiou et al. published a meta-analysis in 2010 on the efficacy and safety of opioid intake in chronic non-cancer pain.[2] Constipation, nausea, and dizziness represented the top three side effects, with a prevalence between 22% and 30%. However, obstructive or central apnea/hypopnea, hypoventilation during sleep, and impairment of respiratory drive remained unmentioned.[2]

Can general practitioners, pain therapists and oncologists reassure their patients regarding respiratory side effects in long-term treatment with opioids?

It is without doubt, that for far too long sufficient palliation has been withheld from pain patients, in fear of side effects, addiction, and misuse of opioids. However, improved knowledge combined with changing attitudes has helped to normalize the use of the most important relievers of pain, leading to a large increase in opioid prescription.[3,4] Moreover, opioids are prescribed not only to relieve pain, but also, for example to alleviate dyspnea in patients with chronic pulmonary disorders.[5] Finally, opiate addiction remains a growing and largely unsolved problem, leading to the incorporation of an increasing number of patients world-wide in methadone maintenance programs.[6] Bearing in mind this widened use of opioids, observations of sleep related breathing disorders (SRBD) are alarming. Kelly et al. described fatal or life-threatening events in children who underwent adenotonsillectomy for obstructive sleep apnea. These children possessed genetic alterations that led to an increased morphine production from codeine.[7] Many such reports of perioperative complications in sleep apnea patients have been published.

In 2007 the broad spectrum of SRBD under opioids were described retrospectively by Walker et al.[8] Besides obstructive disturbances, they found central apneas, ataxic or irregular respiration, and periods of sustained hypoventilation.

However, we have to admit frankly that our knowledge of the pathophysiology of opioid-induced sleep apnea is still very limited. Pattinson reviewed the control of respiration under opioid intake.[9] The author pointed out that respiration becomes shallow and irregular leading to hypercapnia and hypoxia. The respiratory disturbances differed according to the mode of application. Whereas rapid intravenous boli induced apneas, long-term infusions led to a gradual increase of hypercapnia, thereby contributing to the maintenance of respiration. The effect of opioids on the respiratory rhythm has not been conclusively explored. Peripheral and central chemosensitivity play a major role, leading to a reduction of the hypoxic and hypercapnic ventilatory response. However, the extent of the interference and the precise location of the interception of the reflexes are unclear. This retards the pharmaceutical development of opioids with sufficient analgesic properties but minimized respiratory side effects.

Having said all this, physicians will mostly be interested in data relating to the clinical presentation, optimal diagnosis, and treatment of opioid-induced sleep apnea. Are there specific signs and symptoms of opioid induced sleep apnea? They are certainly associated with dizziness, impaired concentration, and daytime sleepiness. But is it possible to differentiate between central nervous system effects and breathing disturbances? Generally speaking, sleepiness and deficits in neurocognitive parameters cease during long-term application, so that even driving may be permitted. However, this trend is not to be expected in SRBD. Another clinically relevant but unsolved problem is the question of whether the outcome of opioid users with or without SRBD differs.

In this current issue, Ramar et al.[10] present an important study focusing on the question of the best available therapy of respiratory disturbances during sleep. They investigated patients with central breathing disturbances due to chronic heart failure or chronic opioid use, who had failed to respond to treatment with constant CPAP. Adaptive servoventilation (ASV) enabled sufficient therapy in the majority of heart failure and opioid patients. The study provides preliminary data, as it was retrospective and a randomized comparison with CPAP, placebo, or optimal pharmaceutical therapy is missing. Nevertheless, the authors analyze the largest sample to date from everyday practice, and in that sense, it is representative of the real-life situation.

In 2008 two studies with contradictory results were published in this journal.[2] While Farney failed to show a differ-

ence between CPAP and ASV, Javaheri found an effective treatment with ASV in a small group of opioid induced sleep apnea patients. The latter results, now being proven by Ramar's data, could be expected due to the algorithm of adaptive servoventilation. CPAP may interfere with SRBD in several ways: it stabilizes the upper airways and counterbalances upper airway obstruction; the positive thoracic pressure reduces left ventricular cardiac afterload and therefore improves the ejection fraction; and finally, CPAP can enlarge lung volumes and reduce ventilation- perfusion mismatch. However, CPAP does not influence, or only marginally influences breathing rhythm and chemosensitivity. In contrast, ASV combines the effects of CPAP (positive expiratory pressure) with variable pressure support and the application of mandatory breaths. Therefore, disturbances of respiratory drive and periods of hypoventilation can be counterbalanced. Interestingly, a higher bicarbonate level was a predictor of ASV success. This surprising finding could have, as discussed by the authors, technical reasons. However, it could also indicate extensive periods of hypoventilation as a part of the SRBD. Based on Ramar's data, the question remains why 30% to 40% of patients with heart failure or opioid induced sleep apnea, respectively, could not be treated optimally. The choice or setting of the device, the mode of reaction of the algorithm, and interface problems may contribute to this phenomenon. However, the results suggest an advantage to the early use of adaptive servoventilation after optimal medical therapy.

Sleep specialists should try to avoid repeating history. The epochal invention of CPAP by Sullivan led to a rather generalized perception of obstructive sleep apnea, but importantly at the same time, to the implementation of the optimal treatment. This coincidence—although of huge value for the patient—handicapped detailed exploration of the pathophysiological background. Opioid-induced sleep apnea is, as pointed out above, even more unclear. Increasing evidence in this field suggests a treatment advantage with adaptive servoventilation. However, all efforts should be undertaken to better understand the clinical presentation, pathophysiology, and prognosis. Opioid-induced sleep apnea is a real problem as the rapidly increasing prevalence indicates. We are however a long way from truly understanding its relevance.

Future studies should try to characterize the different phenotypes of breathing disturbances as precisely as possible. This also has implications for coming guidelines.

CITATION

Randerath WJ; George S. Opioid-induced sleep apnea: is it a real problem? *J Clin Sleep Med* 2012;8(5):577-578.

REFERENCES

1. The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. *Clin J Pain* 1997;13:6-8.
2. Papaleontiou M, Henderson CR Jr., Turner BJ, et al. Outcomes associated with opioid use in the treatment of chronic noncancer pain in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc* 2010;58:1353-69.
3. Sullivan MD, Edlund MJ, Fan MY, et al. Trends in use of opioids for non-cancer pain conditions 2000-2005 in commercial and Medicaid insurance plans: the TROUP study. *Pain* 2008;138:440-9.
4. Caudill-Slosberg MA, Schwartz LM, Woloshin S. Office visits and analgesic prescriptions for musculoskeletal pain in US: 1980 vs. 2000. *Pain* 2004;109:514-9.
5. Rocker G, Horton R, Currow D, Goodridge D, Young J, Booth S. Palliation of dyspnoea in advanced COPD: revisiting a role for opioids. *Thorax* 2009;64:910-5.
6. Sharkey KM, Kurth ME, Anderson BJ, Corso RP, Millman RP, Stein MD. Obstructive sleep apnea is more common than central sleep apnea in methadone maintenance patients with subjective sleep complaints. *Drug Alcohol Depend* 2010;108:77-83.
7. Kelly LE, Rieder M, van den Anker J, et al. More codeine fatalities after tonsillectomy in North American children. *Pediatrics* 2012;129:e1343-7.
8. Walker JM, Farney RJ, Rhondeau SM, et al. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. *J Clin Sleep Med 2007*;3: 455-61.
9. Pattinson KT. Opioids and the control of respiration. *Br J Anaesth* 2008;100:747-58.
10. Ramar K; Ramar P; Morgenthaler TI. Adaptive servoventilation in patients with central or complex sleep apnea related to chronic opioid use and congestive heart failure. *J Clin Sleep Med* 2012;8:569-76.
11. Javaheri S, Malik A, Smith J, Chung E. Adaptive pressure support servoventilation: a novel treatment for sleep apnea associated with use of opioids. *J Clin Sleep Med* 2008;4:305-10.
12. Farney RJ, Walker JM, Boyle KM, Cloward TV, Shilling KC. Adaptive servoventilation (ASV) in patients with sleep disordered breathing associated with chronic opioid medications for non-malignant pain. *J Clin Sleep Med* 2008;4:311-9.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication September, 2012
Accepted for publication September, 2012
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DISCLOSURE STATEMENT

Dr. Randerath has received speaking fees and research support from Weinmann, Respironics, Resmed, Heinen und Löwenstein. Sandhya George has indicated no financial conflicts of interest.