Central Sleep Apnea Induced by Acute Ingestion of Opioids *

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in the heart, the lesion is fully covered by 3 months.[15] A similar interval was noted in the bronchus in both of our patients. Although the different methods available for BPF closure cannot be prospectively evaluated, our findings suggest that the technique of endobronchial ASD occluder implantation may be suitable for large BPFs that originate in the main bronchi, especially when there is a direct and easy pathway for maneuvering.

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References

1 Nagahiro I, Aoe M, Sano Y, et al. Bronchopleural fistula after lobectomy for lung cancer. Asian Cardiovasc Thorac Ann 2007; 15:45–48
2 Lois M, Noppen M. Bronchopleural fistula: an overview of the problem with special focus on endoscopic management. Chest 2005; 128:3955–3965
3 Cerfoliio RJ. The incidence, etiology and prevention of postresectional bronchopleural fistula. Semin Thorac Cardiovasc Surg 2001; 13:3–7
4 McManigle JE, Fletcher GL, Tenholder MF. Bronchoscopy in the management of bronchopleural fistula. Chest 1990; 97:1235–1238
5 Malave G, Foster ED, Wilson JA, et al. Bronchopleural fistula: present day study of an old problem. Am Thorac Surg 1971; 11:1–10
6 Pierson DJ, Horton CA, Bates PW. Persistent bronchopleural fistula air leak during mechanical ventilation: a review of 39 cases. Chest 1986; 90:321–323
7 Hankins JR, Miller JE, Attar S, et al. Bronchopleural fistula: 13 year experience with 77 cases. J Thorac Cardiovasc Surg 1978; 76:755–762
8 Sirbu H, Busch T, Aleksic I, et al. Bronchopleural fistula in the surgery of non-small cell lung cancer: incidence, risk factors and management. Ann Thorac Cardiovasc Surg 2001; 7:330–336
9 Sonobe M, Nawkagawa M, Ichinose M, et al. Analysis of risk factors in bronchopleural fistula after pulmonary resection for primary lung cancer. Eur J Cardiothorac Surg 2000; 18:519–523
10 PauL S, Talbot SG, Carty M, et al. Bronchopleural fistula repair during Clagett closure utilizing a collagen matrix plug. Ann Thorac Surg 2007; 83:1519–1521
11 Tao H, Araki M, Sato T, et al. Bronchoscopic treatment of postpneumonectomy bronchopleural fistula with collagen screw plug. J Thorac Cardiovasc Surg 2006; 132: 99–104
12 Ferguson JS, Sprenger K, Van Natta T. Closure of a bronchopleural fistula using bronchoscopic placement of an endobronchial valve designed for the treatment of emphysema. Chest 2006; 129:479–481
13 Matitiau A, Birk E, Kachko L, et al. Transcatheter closure of secundum atrial septal defects with the Amplatzer septal occluder: early experience. Isr Med Assoc J 2001; 3: 32–35
14 Butera G, Chessa M, Carminati M. Percutaneous closure of ventricular septal defects. Cardiol Young 2007; 17:243–253
15 Han YM, Gu X, Titus JL, et al. New self-expanding patent foramen ovale occlusion device. Catheter Cardiovasc Interv 1999; 47:370–376

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Mohammed Mogri, MD; Mohammed I. A. Khan, MD; Brydon J. B. Grant, MD, FCCP; and M. Jeffrey Mador, MD

Objectives: **Three cases are presented in which patients were using opioids as required for nonmalignant pain management and significant central sleep apnea developed. Patients in the first two cases had no evidence of sleep-related breathing disorders on polysomnography until they ingested an opioid for treatment of chronic pain during the night and severe central sleep apnea developed. The patient in our third case had established obstructive sleep apnea but experienced a significant number of central events after the ingestion of an opioid analgesic, leading to worsening severity of his underlying sleep-related breathing disorder.**

Conclusion: **The short-term ingestion of opioid analgesics can precipitate central sleep apnea in patients with chronic pain receiving long-term opiate therapy who otherwise show no evidence of central sleep apnea and have no cardiac or neurologic disease that would predispose them to central sleep apnea.**

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Key words: central sleep apnea; chronic pain; complex sleep apnea; opioids; sleep apnea

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; CAI = central apnea index; CPAP = continuous positive airway pressure

Our understanding of the effects of opioids on sleep-related breathing disorders is in a state of evolution. Robinson et al[1] showed in 1987 that in healthy individuals without suspected sleep apnea, the use of oral narcotics in standard dosages did not appear to increase sleep-related breathing disorders significantly. However, it is clear that the control of breathing can be compromised by hypnotics, sedatives, and opioids.[2,3] Farney et al[4] reported ataxic breathing, central apneas, sustained hypoxemia, and prolonged obstructive hypopneas in patients receiving long-term therapy with sustained-release opioid medications.

In a prior study,[5] we have observed that patients receiving long-term therapy with opioids for the treatment of chronic pain have an increased prevalence of central

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apnea, obstructive apnea, and combined obstructive and central sleep apnea. We have observed that opioids may complicate underlying sleep apnea and make continuous positive airway pressure (CPAP) therapy less effective.[6] The variability in the use of these agents on an as-needed basis poses an additional challenge as the severity and type of sleep apnea might vary significantly from night to night depending on overall opiate usage.[7] In this series, we report on three patients who had either no evidence of sleep-related breathing disorders or only obstructive sleep apnea despite receiving long-term pain therapy until they ingested an opioid as-needed for pain relief during the night and severe central sleep apnea developed.

Sleep Studies

Overnight polysomnography was performed using standard techniques.[8] A nasal pressure transducer was used to measure airflow. Hypopneas were scored by a visible reduction in airflow lasting at least 10 s that was associated with either a 4% reduction in oxygen saturation or an EEG arousal. An arousal was defined according to the criteria proposed by the Atlas Task Force.[9] Study results were considered to be positive for sleep apnea if the apnea-hypopnea index (AHI) was > 10 events per hour, equivocal for sleep apnea if the AHI was 5 to 10 events per hour, and negative for sleep apnea if the AHI was < 5 events per hour. Respiratory events were first scored manually by an experienced scorer, and then the study was reviewed and corrected by a board-certified sleep physician. Each study was reviewed for potential upper airway resistance events by looking for changes in the contour of the nasal pressure signal, and by examination of the rib cage and abdominal signals for a paradoxical motion in the absence of a defined event.

Case Reports

Case 1

A 57-year-old woman with a body mass index (BMI) of 33 kg/m^2 presented with excessive daytime sleepiness, snoring, and vaguely described choking/gasping arousals at night. Her Epworth sleepiness score was increased (15/24). There was no history or physical findings of heart or neurologic disease, and an echocardiogram revealed normal left ventricular function. The patient's serum bicarbonate concentration was 29 mEq/L. The patient underwent diagnostic nocturnal polysomnography, the results of which were borderline for sleep apnea (*ie*, an AHI of six events per hour without evidence of significant hypoxemia, increased arousals, evidence of hypoventilation, or alteration in the nasal pressure contour that would suggest airflow limitation). The patient continued to remain symptomatic. At this time, a multiple sleep latency test with a prior overnight polysomnography was scheduled as part of further workup. Apart from these complaints, the patient reported chronic back pain and arthralgias in her lower extremities bilaterally, for which she was prescribed 10 mg of oxycodone prn with a maximum daily dosage of 40 mg. During her second sleep study, the patient was noted to ingest an unknown amount of oxycodone for pain at 2:30 AM. While the overall AHI for her second study was 33.6 events per hour, the AHI after ingestion of oxycodone was 92.5 events per hour compared to 3.3 events per hour before the ingestion of oxycodone (Table 1). The patient had a total of 189 apneas and hypopneas after the ingestion of oxycodone, of which 82.5% were central in nature. The central events were not associated with a significant increase in the number of arousals, nor were there significant changes in sleep pattern or oxygen saturation.

Case 2

A 41-year-old woman (BMI, 34 kg/m^2) was referred with complaints of excessive daytime sleepiness, morning headaches, reduced energy during the day, nocturia, snoring, and witnessed apneas. Her Epworth sleepiness score was increased (13/24). There was no history or physical findings suggestive of heart or neurologic disease. Her other medical issues included chronic back and left knee pain. She had undergone numerous surgical procedures for these problems and now was receiving high doses of analgesics for pain control. Medications included methadone (20 mg twice daily) with an extra 10-mg dose at noon, and a combination medication consisting of oxycodone, 7.5 mg, acetaminophen, 325 mg, lamotrigine, 200 mg once daily, and piroxicam, 40 mg once daily (Percocet; Endo Pharmaceuticals; Chadds Ford, PA). The results of the sleep study were within normal limits during the first portion of the night. While the patient's overall AHI was 15.5 events per hour; all events except two hypopneas occurred after 3:00 AM (Fig 1). It was noted by the sleep technician that the patient took two pills of the prescribed combination medication

Table 1—*Respiratory Parameters Before and After Opiate Ingestion

Parameters	Patient 1		Patient 2		Patient 3	
	Before Ingestion	After Ingestion	Before Ingestion	After Ingestion	Before Ingestion	After Ingestion
AHI	3.3	92.5	0.6	27.9	38.1	120.2
CAI	0	76.3	0	27.6	2.1	75.6
AHI						
Non-REM sleep	3.1	112.7	0	31.9	38.1	78.1†
REM sleep	4.0	0	9.8	4.6	0‡	0†
Cycle length, s		20–25		29–32		24–27
Arousal index	4.4	7.8	11.3	27.0	27.6	21.1
O_2 nadir, %	77.2	85.1	85.4	85.2	68.6	59.8§

*REM = rapid eye movement.
†CAI during non-REM and REM sleep shown for patient 3, who had combined obstructive-central sleep apnea.
‡No REM sleep was seen during this portion of the study.
§O_2 nadir was seen after the administration of opiates in patient 3 during obstructive events during REM sleep.

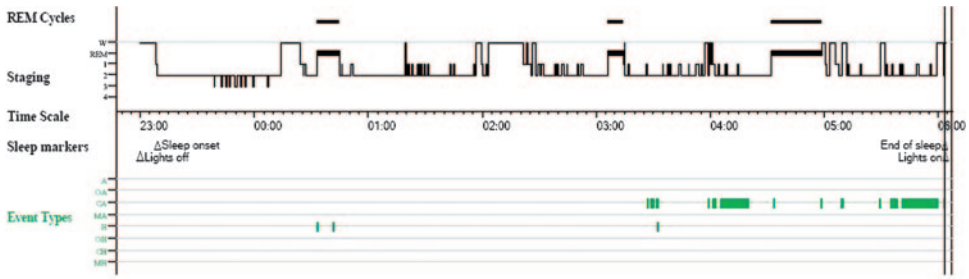

FIGURE 1. Sleep stages, time scale, and event types for case 2. Notice that all the central apneas occurred after 2:00 AM. W = wake; REM = rapid eye movement; A = apnea; OA = obstructive apnea; CA = central apnea; MA = mixed apnea; H = hypopnea; OH = obstructive hypopnea; CH = central hypopnea; MH = mixed hypopnea.

(Percocet; Endo Pharmaceuticals) at 2:00 AM. After ingestion of the opioid, the patient experienced 92 events, of which all but 1 were central apneas (Fig 2). The central apnea index (CAI) was 27.6 events per hour after the ingestion of the oxycodone/acetaminophen combination (Table 1). The central events were associated with an increased total number of arousals but were not associated with changes in sleep pattern or oxygen saturation.

Case 3

A 57-year-old man (BMI, 34.2 kg/m^2) with a history of obstructive sleep apnea was referred with persistent symptoms of excessive daytime somnolence, snoring, gasping/choking arousals, nocturia, and apnea spells. The patient had coronary artery disease, but there was no history or physical findings suggestive of heart failure or neurologic disease. The serum bicarbonate level was 25 mEq/L. The Epworth sleepiness score was increased at 24/24. The patient also reported chronic neck pain and radiculopathy for which he was receiving extended-release morphine, 120 mg three times daily. The patient stated that he took a dose of his extended-release pain medication at midnight during his nocturnal polysomnogram. At 2:00 AM, the patient started to have an increased frequency of central apneas, which correlates with the onset of action for the analgesic effects of extended-release morphine. The overall AHI was 76.3 events per hour with an AHI of 38.1 events per hour before ingestion of the opiate and 120.2 events per hour after ingestion of the opiate (Table 1). His CAI was 2.1 events per hour before the ingestion of morphine, compared to 75.6 events per hour after the ingestion of morphine. These central events were not associated with a significant increase in the number of arousals, nor were there significant changes in sleep pattern or oxygen saturation.

DISCUSSION

Opioids are commonly prescribed for the management of both acute and chronic pain.[10,11] The use of these agents is increasing in the United States.[12] The opioid receptors responsible for the analgesic effect are found in nuclei that are also active for sleep regulation,[13] and hence are thought to be involved in sleep induction and maintenance.[14]

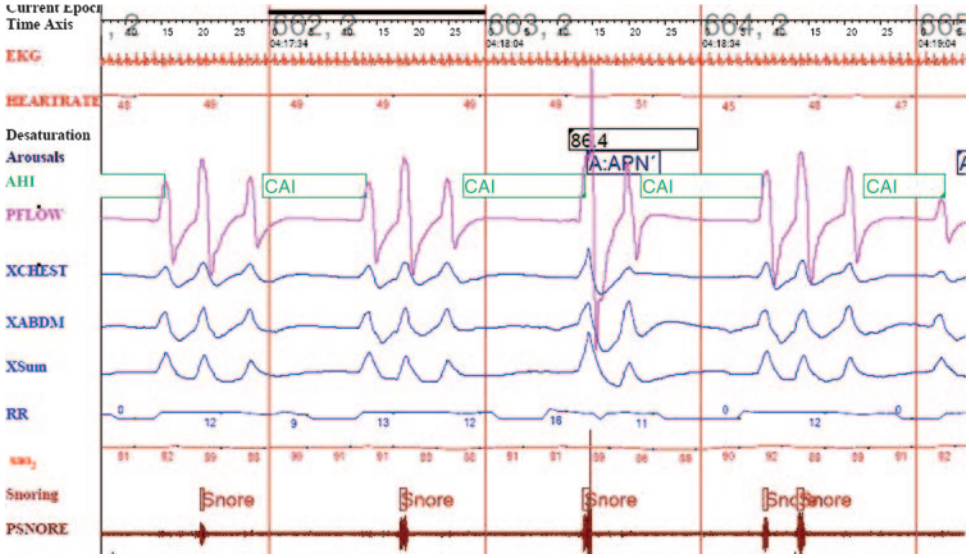

FIGURE 2. Shows multiple central apneas experienced by the patient in case 2. PFLOW = nasal pressure; XCHEST = chest excursion; XABDM = abdominal excursion; XSum = combined chest and abdominal excursion; RR = respiratory rate; SaO_2 = arterial oxygen saturation; PSNORE = snore transducer; EKG = ECG; APN = arousal secondary to apnea; A = arousal.

Long-term opioid use has been previously studied[15] and has been shown to be related to sleep-related breathing disorders. Central sleep apnea was found in 30% of patients receiving methadone maintenance therapy for substance abuse, and the CAI for these patients was significantly correlated with the blood methadone concentration.[2] In an observational study[5] of 140 patients with chronic pain who were receiving opioid therapy, an increased incidence of central apnea, obstructive apnea, and mixed obstructive/central sleep apnea was noted, with a direct relationship between AHI and CAI and the daily dosage of methadone. However, the literature assessing acute opioid use and respiratory disturbances during sleep is scarce.[15] Robinson et al[1] showed that in individuals who had no evidence of sleep apnea, oral hydromorphone in doses of 2 or 4 mg did not increase the incidence of sleep-related breathing disorders. The administration of morphine in otherwise healthy individuals did not increase respiratory disturbances during sleep when compared to their baseline or placebo use.[16] Roth et al[3] concluded that while opioids exacerbate sleep apnea, they do not cause sleep-related breathing disorders *de novo*.

Despite long-term opiate use in patients 2 and 3 and long-term use as needed in patient 1, our patients did not have significant central sleep apnea until they took an additional pain pill at night, at which point severe central sleep apnea developed, at least in terms of the AHI. None of the patients had any cardiac or neurologic disease that would predispose them to central sleep apnea. This finding points out the lability of sleep apnea in these patients, which is highly relevant since patients with chronic pain tend to adjust their pain medicine based on their level of pain. This concept is shown in case 1 where the patient had an equivocal nocturnal polysomnogram when she did not receive any pain medications but significant and severe central sleep apnea developed after the ingestion of an opioid analgesic during the night. The patient in case 2 who was receiving long-term opioid therapy showed no evidence of respiratory disturbances during sleep until she took an additional modest dose of an opioid during the night. The patient in our last case had established obstructive sleep apnea. However, on ingesting an opioid during the night a significant number of central events developed, which added to the severity of his disease.

There is not a lot of information on the mechanisms responsible for central sleep apnea in patients receiving opiates nor is there much information on treatment. In terms of patterns, the central sleep apnea associated with opiates does not usually show a crescendo-decrescendo pattern and has a shorter cycle length (around 30 s)[15] than the central sleep apnea seen in patients with congestive heart failure (cycle length, around 60 s) [Fig 2]. Stable methadone patients have a reduced hypercapnic ventilatory response but an enhanced hypoxic response,[2] which may promote breathing pattern instability. Opioids are well known to suppress central respiratory controllers, which may also promote respiratory pattern instability. Methadone concentration correlates with the CAI,[5] which would certainly be consistent with a direct effect on central respiratory controllers. Other drugs that are often administered to the patient with chronic pain, such as sedatives and antidepressants, may act in concert to promote central sleep apnea. A dose-response relation was found between the CAI and the diazepam equivalent dosage in a prior study of patients with chronic pain.[5]

The consequences of central sleep apnea in this patient population are unknown. The central events do not usually result in oxygen desaturation or substantially alter sleep pattern,[15] as was seen in our patients. The effect on arousals was variable in our patients. Patients receiving therapy with opiates are often sleepy, and whether the central events contribute to this subjective sleepiness remains to be determined. Patients receiving opiate therapy for the treatment of chronic pain have an increased incidence of death. Whether central sleep apnea contributes in any way to this phenomenon remains to be explored.

CPAP is usually ineffective for the treatment of central sleep apnea in these patients. Oxygen therapy can be effective in some patients.[7] In our experience, treatment with bilevel positive airway pressure, with a backup rate (*ie*, the respiratory rate set for the bilevel positive airway pressure device, which will deliver breaths to the patient if the patient's spontaneous breathing rate falls below the set rate) if necessary, is usually effective in alleviating central sleep apnea in these patients.[7] Servoadaptive ventilation is an attractive treatment modality on theoretical grounds, but observational studies in which this modality has been used in this patient population are lacking.

In conclusion, we have shown that the addition of a single dose of opiates at night can precipitate central sleep apnea in patients receiving opiate therapy who otherwise did not display sleep-related breathing disorders. These disturbances were mostly central in nature and could pose management challenges given the ineffectiveness of CPAP therapy in eliminating central events in patients receiving opiates. Further larger-scale studies are required to assess the clinical significance of this finding.

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References

1 Robinson RW, Zwillich CW, Bixler EO, et al. Effects of oral narcotics on sleep-disordered breathing in healthy adults. Chest 1987; 91:197–203
2 Wang D, Teichtahl H, Drummer O, et al. Central sleep apnea in stable methadone maintenance treatment patients. Chest 2005; 128:1348–1356
3 Roth T, Roehrs T, Zorick F, et al. Pharmacological effects of sedative-hypnotics, narcotic analgesics, and alcohol during sleep. Med Clin North Am 1985; 69:1281–1288
4 Farney RJ, Walker JM, Cloward TV, et al. Sleep-disordered breathing associated with long-term opioid therapy. Chest 2003; 123:632–639
5 Webster L, Choi Y, Desai H, et al. Sleep disordered breathing and chronic opioid therapy. Pain Med 2008 (in press)
6 Veeramachaneni S, Choi Y, Desai H, et al. Titration with auto-CPAP in patients with obstructive sleep apnea [abstract]. Am J Respir Crit Care Med 2007; 175:A172
7 Veeramachaneni S, Mador M, Desai H, et al. Effect of

therapy in patients on opioid medications with central sleep apnea [abstract]. Sleep 2007; 30:A188
8 Mador MJ, Kufel TJ, Magalang UJ, et al. Prevalence of positional sleep apnea in patients undergoing polysomnography. Chest 2005; 128:2130–2137
9 Atlas Task Force. EEG arousals, scoring rules and examples: a preliminary report from the Sleep Disorders Task Force of the American Sleep Disorders Association. Sleep 1992; 15:173–184
10 Gutstein H, Akil H. Opioid analgesics. In: Hardman JG, Limbird LE, Gilman AG, eds. Goodman and Gilman's the pharmacological basis of therapeutics. 11th ed. New York, NY: McGraw-Hill, 2005
11 Zech DF, Grond S, Lynch J, et al. Validation of World Health Organization guidelines for cancer relief: a 10 year prospective study. Pain 1995; 63:65–76
12 US Department of Justice, Drug Enforcement Administration. Automation of reports and consolidated order system (ARCOS) 2: report 7. Available at: http://www.deadiversion.usdoj.gov/arcos/retail_drug_summary. Accessed March 26, 2008
13 Aghajanian GK. Tolerance of locus coeruleus neurons to morphine and suppression of withdrawal response by clonidine. Nature 1978; 276:186–188
14 Wilson L, Dorosz L. Possible role of the opioid peptides in sleep. Med Hypotheses 1984; 14:269–280
15 Wang D, Teichtahl H. Opioids, sleep architecture and sleep-disordered breathing. Sleep Med Rev 2007; 11:35–46
16 Shaw IR, Lavigne G, Mayer P, et al. Acute intravenous administration of morphine perturbs sleep architecture in healthy pain-free young adults: a preliminary study. Sleep 2005; 28:677–682

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