Respiratory and Sleep Effects of Remifentanil in Volunteers with Moderate Obstructive Sleep Apnea

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Background: There is concern that opioid-based analgesia will worsen sleep-related respiratory insufficiency in patients with obstructive sleep apnea (OSA), resulting in serious morbidity or mortality. However, there are no studies that directly address the merit of this concern. Consequently, the authors designed this study as the first prospective, double-blind, placebo-controlled investigation of opioid pharmacology in patients with documented OSA.

Methods: Patients (n = 19) with moderate OSA documented by polysomnography (sleep study) were randomized to undergo an additional sleep study while receiving either a saline infusion or a remifentanil infusion ($0.075 \ \mu g \cdot kg^{-1} \cdot h^{-1}$). Sleep stages, apneas, hypopneas, and arterial hemoglobin oxygen saturation were continually recorded during saline or remifentanil infusion, and were compared with values obtained during the patients' earlier sleep study.

Results: Saline infusion had no effect on sleep or respiratory variables. In contrast, remifentanil increased Stage 1 sleep, markedly decreased rapid eye movement sleep, increased arousals from sleep, and decreased sleep efficiency. Remifentanil actually decreased the number of obstructive apneas, but markedly increased the number of central apneas. Arterial hemoglobin oxygen saturation was also significantly lower in OSA patients receiving remifentanil.

Conclusions: The decrease in obstructive apneas likely resulted from the marked decrease in rapid eye movement sleep caused by remifentanil. Despite fewer obstructions, OSA was worse during remifentanil infusion because of a marked increase in the number of central apneas. These data suggest that caution is warranted when administering opioids to subjects with moderate OSA, but that the primary risk may be central apnea, not obstructive apnea.

OBSTRUCTIVE Sleep Apnea (OSA) is a form of sleep disorder breathing in which patients experience intermittent periods of apnea and/or hypopnea, usually (although not exclusively) as a result of complete or partial airway obstruction. These apneic and/or hypopneic episodes result in intermittent hypercarbia and/or hypoxemia, which is associated with significant cardio- and cerebrovascular morbidity including stroke, myocardial ischemia, pul-

monary hypertension, and heart failure.[1–4] The prevalence of OSA varies depending on the criteria used for diagnosis, but approximately 9% of women and 27% of men between the ages of 30 and 60 experience more than 5 apneic or hypopneic episodes per hour of sleep.[5]

Apneas and hypopneas are terminated when the patient arouses sufficiently to relieve the airway obstruction, at which time the respiratory drive is generally increased in response to hypercarbia and/or hypoxemia and the patient transiently hyperventilates to restore normal arterial partial pressure of carbon dioxide (Pa_{CO_2}) and arterial partial pressure of oxygen (P_aO_2). Because opioids decrease the ventilatory response to hypercarbia and hypoxia,[6] concern has been expressed that administering opioids to patients with OSA increases the risk that their ventilatory response to the episodic increases in Pa_{CO_2} and/or decreases in P_aO_2 will be insufficient to reestablish normal arterial gas tensions after obstruction is relieved. Consequently, OSA patients are viewed by some as uniquely vulnerable to significant respiratory morbidity or mortality if given opioids.[7–10] In fact, several manuscripts aimed at educating anesthesiologists about the appropriate perioperative care of patients with OSA have warned of the risk of administering opioid analgesics to these patients because of an assumed negative effect on the frequency and/or severity of apneas and hypopneas during sleep.[7–9] Unfortunately, these recommendations are not based on any studies of opioid effects in patients with OSA.

The perioperative care of OSA patients was more formally addressed by the Clinical Practice Review Committee of the American Academy of Sleep Medicine.[11] This group concluded, "Scientific literature regarding the perioperative risk and best management techniques for obstructive sleep apnea patients is scanty and of limited quality. There is insufficient information to develop an AASM standards of practice recommendation."

The American Society of Anesthesiologists' Task Force on Perioperative Management of Patients with Obstructive Sleep Apnea also reviewed the available scientific literature to provide guidance for the perioperative care of patients with OSA.[10] Like the American Academy of Sleep Medicine, the American Society of Anesthesiologists' Task Force concluded that the scientific literature was inadequate to permit evidence-based recommendations for the care of patients with OSA. However, unlike the American Academy of Sleep Medicine, the American Society of Anesthesiologists' Task Force did write guidelines for the care of this patient population. Although the Task Force's recommendations are well-intentioned and

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well-reasoned, they are not "evidence-based" because the relevant scientific data simply do not exist.

Consequently, we designed this investigation as the first prospective, double-blind, placebo-controlled study to investigate the respiratory and sleep effects of opioids in patients with OSA. The specific hypothesis to be tested was that opioids would increase the number and severity of apneic and hypopneic episodes in patients with moderate OSA.

Materials and Methods

The Virginia Mason Medical Center's Institutional Review Board (Seattle, Washington) approved this study, and all patients gave written informed consent.

Patient Selection and Group Assignment

Patients were recruited from advertisements in the Sleep Disorders Center at Virginia Mason Medical Center. Patients were eligible for this study if they had moderate OSA diagnosed by polysomnography (sleep study) performed at Virginia Mason Medical Center within the previous 12 months. Moderate OSA was defined as an apnea-hypopnea index (AHI) of 15–30 apneas and/or hypopneas per hour. Patients were excluded from this study if they gave a history of acute or chronic pulmonary disease, coronary artery disease, current pregnancy/breastfeeding, chronic opioid or sedative-hypnotic use, or continuous positive airway pressure (CPAP) use during sleep within 7 days before the study. Patients were also excluded if they had gained or lost more than 10 pounds between their baseline diagnostic sleep study and the research study, or if their OSA symptoms had worsened.

Patient age and weight were obtained from clinic records. Sex was determined by patient report. Body mass index (BMI) was determined by dividing patient weight in kilograms by height in meters squared. Lean body mass was calculated using the sex-specific equations developed by Hume.[12]

All patients had undergone formal polysomnography before study enrollment as part of their workup for OSA. This diagnostic sleep study served as the baseline against which the research sleep study performed for this investigation was compared. Patients who met the criteria for study inclusion were randomly assigned to 1 of 2 research groups for their repeat sleep study: saline infusion (control) or remifentanil (Abbott Laboratories, Abbott Park, IL) infusion. Patients were blinded to their group assignment.

Polysomnography

Attended, in-laboratory polysomnography was performed in Virginia Mason Medical Center's American Academy of Sleep Medicine-accredited Sleep Disorders Center using a standard data acquisition montage that included electroencephalogram, extraoculogram, chin electromyogram, bilateral leg electromyogram, electrocardiogram, pulse oximetry, chest and abdomen movement, and nasal airflow. A single investigator (Douglas F. Schmidt, Ph.D.) who was blinded to the patient's group, scored all sleep studies (baseline diagnostic and research). Sleep was staged from electroencephalogram and extraoculogram data according to the criteria of Rechtschaffen and Kales.[13] Because the distinction between the 2 slow-wave sleep stages (Stage 3 and Stage 4) is arbitrary, the 2 stages are combined when scoring polysomnography studies at Virginia Mason Medical Center. Arousals were scored according to criteria established by the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association.[14] Respiratory events were defined as follows: apnea, cessation of airflow for 10 s or longer; hypopnea, a 30–70% reduction in airflow signal accompanied by either >3% oxygen desaturation and/or arousal. Central apneas are distinguished from obstructive apneas by the absence of respiratory effort. Mixed apneas are defined as apneas having a clear central and obstructive component. The AHI was calculated by adding the total number of apneas and hypopneas and dividing them by the total sleep time.

Cadwell EZ EEG 2.1 equipment and software (Cadwell Laboratories, Inc., Kennewick, WA) were used for all data acquisition.

Protocol

Patients were admitted to the Sleep Disorders Center and Registered Polysomnographic Technologists applied the electrodes and monitors necessary for data acquisition. An IV infusion was started and heparin-locked until the patient felt ready to sleep, at which time an infusion of normal saline (20 ml/h) or remifentanil (0.075 mg/kg lean body mass) was started using a positive pressure Alaris infusion pump (Cardinal Health, Dublin, OH). A bolus loading dose of remifentanil was not administered. Remifentanil or saline infusion and data acquisition continued throughout the night until the patient awoke in the morning.

Patients were continuously monitored by the sleep technologist assigned to the patients. In addition to assuring the integrity of the data collected, the sleep technologist was responsible for determining whether patients had respiratory compromise that was severe enough to warrant intervention. As is the routine in the Virginia Mason Medical Center Sleep Disorders Center, the decision to intervene was made by the sleep technologist in consultation with the Sleep Medicine Physician on call during the study. The type of intervention (waking the patient, administering oxygen, initiating CPAP, and so forth) was determined by guidelines preestablished by the Sleep Disorders Center for all patients

undergoing polysomnography. One or more of the anesthesiologist investigators was continuously present during the study to intervene if any patient developed respiratory compromise that did not respond to the Center's established guidelines.

Intrastudy Nonremifentanil Drug Administration

The Virginia Mason Medical Center Sleep Disorders Center protocol for polysomnography permits oral zolpidem (Sanofi Aventis, Bridgewater, NJ) administration to help induce sleep in sleep study patients who have difficulty initially falling asleep. For the purposes of this study, patients who had been given zolpidem as part of their initial diagnostic sleep study were given it at bedtime for this study. Two patients in the remifentanil group received 5 mg zolpidem at bedtime, and 1 patient in the saline group received 10 mg zolpidem at bedtime.

Patients chronically taking pramipexole (Boehringer-Ingelheim, Ridgefield, CT) at bedtime for restless leg syndrome were permitted to take it the night of the research sleep study if they had taken it during their baseline sleep study. One patient in the remifentanil group took 0.25 mg pramipexole at bedtime.

All data points for the 4 patients who received medications at bedtime fell within the average and 1 SD of their respective group means. Thus, there was no evidence that they were outliers and they were included in all group analyses.

Remifentanil Plasma Assay

After waking in the morning and before stopping remifentanil or saline infusions, venous blood (5–10 ml) was drawn from the arm opposite the IV infusion for measurement of remifentanil plasma concentration. Blood was collected on ice into glass tubes containing 200 μl 50% sodium citrate to prevent remifentanil metabolism in plasma. Within 15 min of collection, samples were spun (3000 x g) at 15°C for 15 min. The resulting plasma was stored at –70°C until analyzed.

Plasma was assayed for remifentanil concentration by the Pain and Toxicity Research Laboratory at the Fred Hutchinson Cancer Research Center in Seattle, Washington using a modification of the method of Egan *et al.*[15,16] Briefly, 0.25 ml plasma was mixed with 1.5 ml 0.1M KH_2PO_4 buffer (pH = 6) and 5 ng fentanyl-d5 (internal standard). Samples were applied to Varian Certify solid phase extraction columns (25 mg) (Varian, Inc., Palo Alto, CA), which had been prewashed sequentially with 2 ml methanol, 2 ml deionized water, and 2 ml phosphate buffer. After drawing the sample through the solid phase extraction tube, the tube was washed sequentially with 2 ml deionized water, 2 ml 1M acetic acid, and 2 ml methanol. The solid phase extraction tube was air dried for 5 min and then eluted with 2 ml methylene chloride: isopropanol:ammonium hydroxide (80:20:2). The eluate was evaporated under a stream of air. The residue was

Table 1. Demographic Information

Parameter	Control Group (n = 9)	Remifentanil Group (n = 10)
Age, y	49 ± 11	50 ± 12
Sex, male:female	5:4	6:4
Body mass index, kg/m^2	36 ± 7	31 ± 8
Time between studies, d	98 ± 86	112 ± 112

reconstituted in 100 μl of high performance liquid chromatography mobile phase (see next paragraph), and 5 μl was injected on the high-performance liquid chromatography system.

Sample extracts were analyzed on an Agilent 1100-series liquid chromatograph/mass spectrometer (Agilent Technologies Inc., Santa Clara, CA). The high-performance liquid chromatography column was a Zorbax SB-C18 150 mm × 2.1 mm × 5μ (Agilent). The mobile phase consisted of 10 mM ammonium acetate (pH = 4) and acetonitrile in a ratio of 60:40. The flow rate was 0.3 ml/min at 40°C. The mass spectrometer was operated in the electrospray ionization plus single-ion monitoring mode, monitoring m/z 342 for fentanyl-d5 and m/z 377 for remifentanil. A standard curve was generated, ranging from 0.2 to 200 ng/ml.

Statistical Analysis

A prospective power analysis was conducted for a single outcome variable (AHI) to determine group size. The assumptions for the power analysis were that alpha = 0.05, power = 0.8, SD = 7, desired detectable difference = 4, and statistical analysis conducted on paired samples and correlation for paired data = 0.8. This analysis indicated that 10 patients were needed for each group. Ten patients were enrolled in each group, but 1 patient dropped out of the control group before they were studied. Therefore, except as noted in the tables, all data are comprised of 9 data points for the control group, and 10 data points for the remifentanil group. In addition, all reported variables are part of a standard sleep study at our institution, and the decision to analyze all variables for statistical significance was made prospectively.

Between-group demographic analyses (table 1) were performed using Student's unpaired *t* test. Except as noted in the following paragraph, all between-group comparisons (saline *vs.* remifentanil infusion) were made by first calculating the difference between the value for the variable of interest obtained during baseline polysomnography, and that during either saline or remifentanil infusion for each subject. These "change" data were then analyzed for statistical significance using Student's unpaired *t* test (normally distributed data) or Mann–Whitney U test (non-normally distributed data). Normally distributed data are reported as average ± SD, and non-normally distributed data as median and interquartile range in tables 2, 3, 4, and 5.

Table 2. Sleep Characteristics

Parameter	Control Group (n = 9)				Remifentanil Group (n = 10)			
	Baseline	Saline	Difference	Difference 95% CI	Baseline	Remifentanil	Difference	Difference 95% CI
Sleep time, min								
Time in bed	485 ± 12	479 ± 10	−7 ± 13	−17 to 3	494 ± 40	474 ± 16	−20 ± 36	−46 to 6
Total sleep time	428 ± 44	426 ± 22	−2 ± 28	−23 to 19	429 ± 35	360 ± 51	−68 ± 65*	−114 to −22
Sleep efficiency, (%)	88 ± 8	89 ± 4	1 ± 6	−3.5 to 5	88 ± 8	76 ± 11	−11 ± 14*	−21 to −1
Sleep latency, min								
Latency to stage 1	8 (3–11)	8 (6–14)	−1 (−3.25 to 8)	−12 to 10	11 (4–19)	13 (7–33)	6 (0–17)	−3 to 19
Latency to stage 2	11 (7–18)	9 (8–17)	−2 (−7 to 5)	−7 to 4	17 (11–26)	40 (27–124)	12.5 (6–113)*	0–105
Latency to stage 3/4	29 (22–35)	34 (22–41)	1 (−15 to 11)	−22 to 40	41 ± 90	[121 ± 197]	[72 (16–180)]	−44 to 238
Latency to REM	122 (76–265)	78 (70–174)	−4 (−74 to 32)	−92 to 48	126 (77–206)	[118 (100–135)]	[44 (19–70)]	−283 to 371
Sleep stage duration, % total sleep time								
Stage 1	6 (4–16)	9 (7–14)	2 (−1 to 5)	−12 to 9	11 (9–13)	29 (18–49)	16 (7–39)*	9–34
Stage 2	50 ± 13	51 ± 11	2 ± 13	−9 to 12	53 ± 8	55 ± 14	3 ± 13	−7 to 12
Stage 3/4	20 ± 12	19 ± 9	−2 ± 9	−11 to 30	16 ± 8	10 ± 15	−6 ± 16	−18 to 6
REM	17 ± 9	21 ± 8	4 ± 9	−3 to 10	20 ± 6	2 ± 5	−17 ± 6*	−21 to −13
Stage changes per h	15 ± 7	19 ± 8	4 ± 6	−1 to 9	20 ± 5	35 ± 14	15 ± 15*	5–26
% having REM sleep	100	100			100	20*		

Baseline, Saline, Remifentanil and Difference data with "±" are mean ± SD. Data without "±" are median and (interquartile range). Difference is the individual difference between baseline and either saline or remifentanil infusion. Square brackets [ ] indicate that the reported data represents few subjects (n = 6 for stage 3/4 sleep and n = 2 for REM); statistical analysis was not performed on these data.

* $P \leq 0.05$.

CI = confidence interval; REM = rapid eye movement.

Because the number of central apneas in the remifentanil group demonstrated a binary distribution, these data were analyzed using a randomization test for matched pairs. Within group differences in the proportion of subjects having rapid eye movement (REM) sleep was analyzed using Fisher's exact test. Data for the frequency of events (*e.g.*, arousals, desaturations, apneas) occurring during REM sleep and remifentanil infusion are reported in the tables but were not analyzed for statistical significance, because only 2 of 10 patients receiving remifentanil had any REM sleep. Similarly, data for the timing (*e.g.*, latency, duration) of stage 3/4 sleep were not analyzed for statistical significance, because only 6 patients receiving remifentanil had stage 3/4 sleep.

Instat and Prism software (both from Graphpad Software Inc., San Diego, CA) were used for all statistical analyses except the matched pairs randomization test, which was performed by Paul Sampson, Ph.D. (Research Professor and Director of the Statistical Consulting Program, Department of Statistics, University of Washington, Seattle, Washington) and his students in the Statistical Consulting Program of the University of Washington Statistics Department. Differences were considered statistically significant if $P \leq 0.05$. No attempt was made to correct for multiple comparisons.

Results

There were no differences between the saline and remifentanil groups in age, BMI, sex distribution, or time

interval between baseline diagnostic sleep study and research study (table 1). Remifentanil plasma concentration averaged 3.4 ± 0.9 ng/ml.

Saline infusion did not alter the patients' sleep architecture, as compared with their baseline diagnostic study (table 2). In contrast, remifentanil infusion significantly decreased sleep efficiency (% of time in bed spent sleeping), increased the latency to Stage 2 sleep, increased the amount of time spent in Stage 1 sleep, decreased the average amount of time spent in REM sleep, increased the number of sleep stage changes per hour, and markedly decreased the number of patients having any REM sleep (table 2).

Saline infusion had no effect on arousals (table 3). In contrast, remifentanil infusion significantly increased both the total number of arousals and the arousal index (table 3).

Saline infusion had no effect on either AHI or on the type of apneas (central *vs.* obstructive) (table 4). In contrast, the number of obstructive apneas was actually decreased significantly by remifentanil infusion, and the number of central apneas was significantly increased (table 4). The severity of apneas and hypopneas, as indicated by their maximum duration, was not altered by remifentanil (table 4).

Interestingly, the increase in the average number of central apneas in the remifentanil group was not uniform across the group. Rather, the increase resulted from very large increases in a subset of 4 patients (fig. 1). The 6 patients who did not have a marked increase in their number of apneas had 0.2 ± 0.3 apneas per

Table 3. Arousal

	Control Group (n = 9)				Remifentanil Group (n = 10)			
Parameter	Baseline	Saline	Difference	Difference 95% CI	Baseline	Remifentanil	Difference	Difference 95% CI
Arousals (total number)								
With respiratory event	91 ± 41	166 ± 114	75 ± 112	−11 to 161	103 ± 36	187 ± 115	84 ± 91	18–149
Nonspecific	144 ± 115	146 ± 85	1.3 ± 155	−118 to 121	125 ± 86	267 ± 134	142 ± 159	28–255
Total (respiratory + nonspecific)	247 ± 121	319 ± 108	72 ± 200	−81 to 226	246 ± 112	459 ± 173	257 ± 218*	68–372
Arousal indices (occurrence per h)								
REM	42 ± 22	42 ± 20	0 ± 31	−23 to 24	32 ± 18	[44 ± 3.4]	[10 ± 18]	[−151 to 170]
Non-REM	36 (15–54)	39 (34–61)	14 (−15 to 35)	−11 to 37	28 (22–46)	87 (46–100)	59 (29–62)	21–67
Total	36 ± 19	45 ± 15	9 ± 30	−13 to 32	35 ± 17	78 ± 29	43 ± 30*	21–64

Baseline, Saline, Remifentanil and Difference data with "±" are mean ± SD. Data without "±" are median and (interquartile range). Difference is the individual difference between baseline and either saline or remifentanil infusion; statistical analysis was performed on these data. Square brackets [ ] indicate that the reported data represent only 2 patients; statistical analysis was not performed on these data.

* $P \leq 0.05$.

CI = confidence interval; REM = rapid eye movement.

hour at baseline, and 0.2 ± 0.2 apneas per hour during remifentanil infusion. The 4 patients whose central apnea index increased dramatically had 0.8 ± 0.9 apneas per hour at baseline, and 43 ± 34 apneas per hour during remifentanil infusion. The number of apneas per hour at baseline did not differ significantly between these 2 subgroups, but the number occurring during remifentanil infusion did ($P = 0.0136$). Of the 4 patients with a markedly increased number of central apneas, 1 had received 5 mg zolpidem at bedtime. This patient had the fewest number of central apneas (71) of the 4. In addition, neither of the 2 patients in the remifentanil group who had REM sleep was among the 4 patients with a markedly increased number of central apneas.

Saline infusion had no effect on any measurement of arterial hemoglobin oxygen saturation (S_aO_2%) (table 5). In contrast, remifentanil significantly decreased the lowest S_aO_2 % reached while awake, during sleep, and during a respiratory event (apnea or hypopnea). The desaturation index and the number of desaturations below 90% were also significantly increased in the remifentanil group. The amount of time spent with S_aO_2 % in the 81–90% range was increased in the remifentanil group, and the amount of time spent with S_aO_2 % in the 91–100% range was correspondingly decreased.

No patient in the saline infusion group required intervention because of respiratory or other problems. Based on the Sleep Disorders Center protocol, 1 pa-

Table 4. Apneas and Hypopneas

	Control Group (n = 9)				Remifentanil Group (n = 10)			
Parameter	Baseline	Saline	Difference	Difference 95% CI	Baseline	Remifentanil	Difference	Difference 95% CI
Apnea-hypopnea index (apneas + hypopneas per h)								
Total sleep time	23 ± 6	34 ± 20	11 ± 17	−2 to 24	24 ± 5	44 ± 29	21 ± 26	2–39
Type of apnea/hypopnea (number per hour)								
Central	0.1 ± 0.3	1 ± 2	1 ± 1	0–1	0.4 ± 1	17 ± 29	17 ± 29*	−4 to 38
Obstructive	9 ± 6	13 ± 14	5 ± 11	−4 to 13	8 ± 5	4 ± 6	−4 ± 5*	−8 to 1
Mixed	0 (0–1)	0 (0–0.4)	0 (0–0.3)	0–0.3	0 (0–0.3)	0 (0–2)	0 (0–2)	−1 to 3
Hypopnea	14 ± 5	21 ± 10	7 ± 13	−3 to 16	15 ± 6	22 ± 16	7 ± 16	−4 to 18
Apnea/hypopnea mean duration (seconds)								
Central	[10 ± 0]	[14 ± 4]	[5 ± 3]	[−2 to 12]	12 ± 2	16 ± 6	−0.4 ± 2	−3 to 2
Obstructive	17 ± 6	18 ± 7	0.3 ± 8.1	−6 to 7	17 ± 6	13 ± 3	−5 ± 5	−9 to −1
Mixed	[13 ± 0.3]	[18 ± 9]	[7 ± 9]	[−15 to 28]	[12 ± 4]	[12 ± 2]	[−2 ± 0]	[−2 to −2]
Hypopnea	18 ± 5	18 ± 7	0.1 ± 7	−9 to 4	18 ± 7	15 ± 4	−3 ± 9	−6 to 6

Baseline, Saline, Remifentanil and Difference data with "±" are mean ± SD. Data without "±" are median and (interquartile range). Difference is the individual difference between baseline and either saline or remifentanil infusion; statistical analysis was performed on these data. Square brackets [ ] indicate that the reported data represent 3 or fewer patients; statistical analysis was not performed on these data.
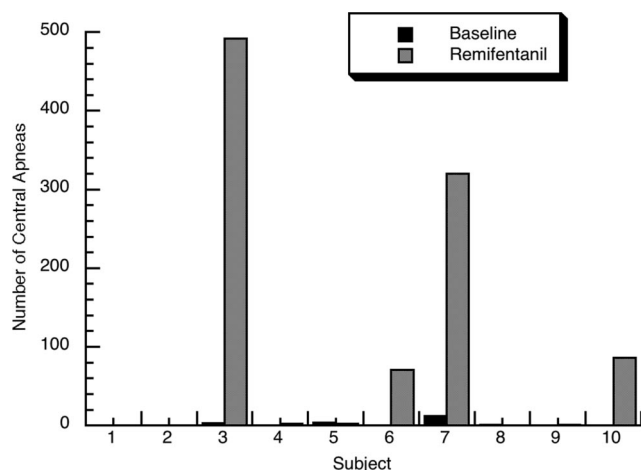
* $P \leq 0.05$.

CI = confidence interval.

Fig. 1. Number of central apneas in the remifentanil group during baseline diagnostic study and during remifentanil infusion. The data have a binary distribution, with the majority of patients having no or very few central apneas during both studies, while a subset of 4 patients had a dramatic increase in the number of central apneas during remifentanil infusion.

tient in the remifentanil group required supplemental oxygen (2 l/min *via* nasal cannula) because of S_aO_2 below 80% for greater than 5 min. This patient was not one of the subgroup with a large increase in central apneas, nor was he 1 of the 2 patients who had REM sleep during remifentanil infusion. He was 1 of the 2 patients who were given zolpidem (5 mg) at bedtime before his baseline study (during which he did not need supplemental oxygen) and before the remifentanil infusion study. This subject's lowest S_aO_2 percentage before receiving supplemental oxygen was included in the statistical analysis, as were the number

of desaturations he experienced; however, the amount of time spent within each saturation range was excluded from analysis.

Discussion

Saline infusion did not significantly alter any sleep study variable. This finding suggests that the presence of an IV and continuous saline infusion does not artificially alter polysomnography. This fact gives us confidence that the findings from the remifentanil group are the result of the opioid's effects, and not a methodological artifact.

Remifentanil was chosen as the opioid for this study purely for pharmacokinetic reasons; *i.e.*, it reaches steady-state plasma concentration in under 10 min,[16] thus our patients had stable plasma concentrations throughout the approximately 7-h study period. In addition, remifentanil has an effect site elimination half-life of less than 4 min once the infusion is stopped,[17] which provides a margin of safety not possible with other opioids. However, we do not think that there is any reason to believe that the data are unique to remifentanil; *i.e.*, an equipotent dose of any opioid would be expected to generate comparable results.

The remifentanil dose used for this study (0.075 μg · kg^{-1}· min^{-1}) was chosen because it falls within the range required to produce effective postoperative analgesia. For example, Bowdle *et al.*[18] reported that 83% of postoperative patients required remifentanil infusion rates between < 0.05 and 0.15 μg · kg^{-1}· min^{-1} to

Table 5. Oximetry

Parameter	Control Group (n = 9)				Remifentanil Group (n = 10)			
	Baseline	Saline	Difference	Difference 95% CI	Baseline	Remifentanil	Difference	Difference 95% CI
Lowest S_aO_2								
While awake	88 ± 5	89 ± 9	1 ± 8	1–8	91 ± 2	82 ± 7	−9 ± 8*	−8 to 6
During sleep	84 ± 4	85 ± 6	1 ± 5	−3 to 5	87 ± 4	80 ± 5*	−6 ± 6*	−10 to −2
During respiratory event	84 ± 4	85 ± 6	1 ± 5	−3 to 5	87 ± 4	81 ± 6	−6 ± 5*	−10 to −2
Desaturation index (number per h)								
Total	6 (2–14)	3 (2–21)	2 (−7 to 7)	−8 to 13	6 (1–9)	15 (3–40)	5 (0–35)	0–29
REM	22 ± 27	21 ± 23	−2 ± 32	−26 to 23	18 ± 19	[4 ± 4]	[−2 ± 12]	[−111 to 106]
Non-REM	6 (1–13)	2 (1–13)	1 (−4 to 3)	−8 to 13	2 (0–8)	15 (3–40)	9 (1–36)	2–32
Desaturations <90% (number)								
Total	10 (3–22)	3 (0–39)	1 (−8 to 18)	−12 to 27	10 (4–19)	106 (50–165)	87 (25–157)*	19–228
REM	7 ± 7	6 ± 11	−2 ± 10	−10 to 6	[7 ± 8]	[5 ± 4]	[−1 ± 4]	[−32 to 31]
Non-REM	2 (0–9)	1 (0–21)	1 (−1 to 12)	−8 to 25	3.5 (0–11)	102 (49–165)	91 (38–159)*	24–235
Time with S_aO_2 in range (min):								
71–80%	0 (0–0)	0 (0–0)	0 (0–0)	−0.1 to 0.1	0 (0–0)	0.05 (0–0.5)	0.05 (0–0.5)	−1 to 2
81–90%	5 ± 5	5 ± 6	0 ± 7	−5 to 5	7 ± 13	86 ± 68	80 ± 67*	31–127
91–100 %	477 ± 15	469 ± 11	−8 ± 13	−18 to 1	485 ± 43	385 ± 70*	−100 ± 77*	−155 to −45

Baseline, Saline, Remifentanil and Difference data with "±" are mean ± SD. Data without "±" are median and (interquartile range). Difference is the individual difference between baseline and either saline or remifentanil infusion; statistical analysis was performed on these data. Square brackets [ ] indicate that the reported data represent only 2 patients; statistical analysis was not performed on these data.

* $P \leq 0.05$.

CI = confidence interval; REM = rapid eye movement; S_aO_2 = arterial hemoglobin oxygen saturation.

maintain pain ratings of zero or mild.[18] Similarly, Yarmush *et al.*[19] reported that $0.125 \pm 0.036\ \mu g \cdot kg^{-1} \cdot min^{-1}$ was the mean remifentanil infusion rate required for successful postoperative analgesia in surgical patients expected to experience moderate to severe pain. Thus, the remifentanil dose used for this study is roughly in the midrange of doses required for effective postoperative analgesia and, in that sense, is a clinically relevant dose. Importantly, our data should not be construed to suggest that all opioid doses will produce similar effects in OSA patients. It is entirely possible that significantly greater or lesser doses would produce qualitatively and or quantitatively different effects. Similarly, our data should not be interpreted to indicate that all patients with OSA will respond similarly. It is entirely possible that subjects with more severe OSA or with different OSA patterns (*e.g.*, central apnea more severe than obstructive apnea) may respond differently.

Remifentanil infusion significantly impaired sleep architecture in these patients with moderate OSA. Of particular clinical importance was the fact that REM sleep was markedly decreased and arousals during respiratory events increased. These findings are consistent with studies of opioid effects on sleep architecture in non-OSA subjects. For example, Kay *et al.* demonstrated that acute administration of 0.43 mg/kg intramuscular morphine to healthy, opioid-naïve volunteers also abolished REM sleep and increased nocturnal awakenings.[20] In a similarly designed study, Shaw *et al.* found that 0.1 mg/kg IV morphine reduced the amount of time spent in slow-wave (*i.e.*, Stage 3 and Stage 4) and REM sleep stages, but did not alter arousal indices.[21] Thus, the effect of opioids on sleep architecture in patients with moderate OSA does not appear to be qualitatively much different than what other investigators have observed in patients without OSA.

Importantly, both the study by Kay and the study by Shaw reported that the moderate opioid doses they studied did not produce any evidence of sleep disordered breathing (apneas or hypopneas) in normal individuals. Similarly, Robinson *et al.* found that 4 mg oral hydromorphone had no effect on the number of apneas or hypopneas experienced by volunteers without OSA. Obviously, a high enough opioid dose will induce apnea in any patient, but the observation by multiple investigators that moderate opioid doses (well within the range typically used for postoperative analgesia) do not produce sleep disordered breathing in normal patients would suggest that our finding of increased AHI in patients with OSA is an indication that these patients may respond differently to opioids than patients without OSA.

Some authors have suggested that opioids would be expected to increase the risk of airway obstruction in patients with OSA.[7] However, our data would suggest that this is not necessarily the case. In fact, we found that remifentanil actually decreased the number of obstructive apneas experienced by our patients with moderate OSA. The most likely explanation for this finding is the fact that remifentanil significantly decreased REM sleep. Pharyngeal muscle tone is generally lowest in REM sleep and consequently airway obstruction is often more prevalent during REM.[22,23] In addition, the fact that remifentanil increased arousals during apneic and hypopneic episodes may explain why the severity of apneas and hypopneas were not increased by remifentanil. Finally, the fact that opioids do not increase airway resistance[6] is also consistent with our findings of fewer obstructions during remifentanil infusion.

Unfortunately, the reduction in obstructive episodes that results from opioid-induced REM suppression may only be temporary, because REM suppression is often followed by a significant increase in REM sleep (REM rebound),[24] which could worsen obstructive episodes. How continued opioid use in the setting of REM rebound might affect obstructive episodes is unknown. However, it gives reason to question the recommendations of the American Society of Anesthesiologists Task Force that observing OSA patients in the postoperative recovery room for a period of time, "preferably while they appear to be asleep," is sufficient to assure "adequacy of postoperative respiratory function" and to then discharge the patient to an unmonitored setting (*i.e.*, home or unmonitored hospital bed).[10]

Our finding that central apneas were dramatically increased in a subset of patients (an observation we term *opioid-emergent central sleep apnea*) is very interesting. Importantly, central apneas in this group were not simply the normal response to moderate opioid doses. As Kay, Shaw and Robinson reported, moderate opioid doses do not produce central apneas in normal patients.[6,20,21] In fact, the majority of OSA subjects receiving remifentanil in this study did not have an increase in the number or duration of central apneas they experienced. Interestingly, the incidence of significant central apneas in our study of acute opioid exposure is comparable to the incidence found in patients chronically taking opioids. For example, Wang *et al.* found that 30% of stable methadone maintenance patients without OSA had central apneas during sleep, albeit at a much lower rate than our patients.[25]

Why a subset of patients had such a dramatic increase in the number of apneas is unclear. To gain some insight into possible risk factors for central apnea during opioid administration, we compared the age, BMI, and remifentanil concentration in the subset of patients who had a significant increase in central apneas with those who did not. The patients with increased central apneas were older (age, 56 ± 11 *vs.* 46 ± 11 y), less obese (BMI, 28 ± 7 *vs.* 33 ± 8) and had a minimally lower remifentanil plasma concentration (3.3 ± 0.8 *vs.* $3.4 \pm 1\ \mu g/ml$). Because of limited statistical power, none of these differences reached statistical significance.

However, lack of statistical significance in the face of inadequate statistical power does not necessarily mean lack of clinical relevance. For example, multiple clinical studies have shown that opioid-mediated respiratory depression in the postoperative period is more common in older patients.[26,27] Thus, the fact that the patients with markedly increased central apneas were an average of 10 y older than those without an increase in central apneas is consistent with data from other studies, and suggests that it is reasonable to hypothesize that increasing age may be a risk factor for central apnea in this patient population. Further studies are necessary to confirm or refute this hypothesis.

The difference in BMI between these 2 subgroups groups is not trivial. Patients who had a significant increase in central apneas would be categorized as overweight by the United States Centers for Disease Control and Prevention, while those without an increase would be classified as obese. The fact that plasma concentrations were nearly identical in those with and without central apneas indicates that calculation of BMI did not introduce a bias that resulted in higher remifentanil plasma concentrations in the lower weight patients. Interestingly, in their study of central apneas in patients without OSA who were chronically taking opioids, Walker *et al.* also found that BMI was *inversely* correlated with central apneas.[28] Thus, as with age, it is reasonable to hypothesize that decreased weight may be a risk factor for central apnea. Additional studies are needed to confirm whether any such relationship really exists.

If central apneas are a major factor contributing to opioid-related respiratory morbidity in patients with OSA, our findings raise several concerns related to the identification and perioperative care of this subset of patients. Specifically, much of the emphasis on identifying patients at risk of OSA, particularly in the American Society of Anesthesiologists' guidelines, is focused on obesity and sleep partner-witnessed apnea.[10] Given that these patients are not necessarily obese, this aspect of screening may not be helpful for identifying patients at risk of central apnea. In addition, because this subset of patients did not have a significant incidence of central apneas in the absence of opioid, they are not likely to be identified by an observant sleep partner. Thus, these patients are less likely to be identified by the American Society of Anesthesiologists Task Force's preoperative screening tool. In addition, if central apneas are a major cause of morbidity for OSA patients in the perioperative period, then the use of CPAP as a means of forestalling opioid-related respiratory complications may not be effective, because while CPAP can prevent obstructive apnea, there is no evidence that it will prevent central apnea. More concerning is the fact that approximately 15% of OSA patients treated with CPAP develop central apneas with the initiation of CPAP.[29-31] This phenomenon is known as CPAP-emergent central sleep apnea, or complex sleep apnea. Whether simultaneous opioid administration will increase the incidence or severity of CPAP-emergent central sleep apnea is unknown, but our data would suggest that there is reason to be concerned that this is a possibility, at least in some patients. The important point is that clinicians should not assume that CPAP will ameliorate all potential harm that opioids may cause to patients with OSA.

A criticism of our study is that it did not include patients who had undergone surgery, so the impact of factors such as residual anesthetic effects and pain are not considered. However, residual anesthetic effects are unlikely to be a significant factor, because brain concentrations of drugs like propofol or volatile anesthetic agents are negligible within a few hours after surgery. In addition, anesthesia and surgery, in and of themselves, do not have major effects on sleep. For example, Moote *et al.* performed sleep studies in nonsurgical volunteers 2 nights before and for 4 nights after 3 h of 1.5 minimum alveolar concentration (MAC) isoflurane anesthesia.[32] Polysomnography demonstrated that isoflurane anesthesia had no effect on REM sleep or Stage 1 sleep. Stage 2 sleep increased, but to a clinically insignificant degree (52 to 60% of total sleep time), on the first postisoflurane night only. There were no sleep changes as compared with baseline on the subsequent 3 nights after isoflurane anesthesia. In addition, Rosenberg-Adamsen *et al.* studied non-OSA patients before and after laparoscopic cholecystectomy to determine the effects of surgery and anesthesia on sleep.[33] Patients had a general anesthetic with isoflurane, nitrous oxide, midazolam, thiopental and "low-dose" fentanyl. Postoperative analgesia was with ibuprofen alone. Similar to the findings of Moote *et al.*, surgery and anesthesia did not alter REM sleep, Stage 1 sleep, or arousals. There was a small increase in Stage 2 sleep (45 to 57% of total sleep) and a decrease in slow-wave sleep (7 to 13% of total sleep). These 2 studies demonstrate that surgery and anesthesia, in and of themselves, do not produce significant effects on sleep. In fact, all of the perioperative sleep disturbances that accompany major surgery (*e.g.*, absent REM sleep, increased Stage 1 sleep, increased arousals) can be explained solely by opioid effects on sleep. Thus, given that OSA is a sleep-dependent phenomenon, one would not expect surgery and anesthesia alone to have significant effects on the manifestations of OSA. Whether pain would alter the effects of opioids on OSA is unknown.

In summary, many patients with recognized and unrecognized OSA receive opioids every day without evident untoward effects. Unfortunately, anecdotal reports suggest that a minority of OSA patients do experience significant respiratory morbidity and occasionally mortality because of opioids prescribed to treat pain. The broad goal of this study was to begin to generate the data necessary to understand the nature of the risks opioids

pose to patients with OSA. Importantly, this study is too small to be used to make specific recommendations for the care of patients receiving opioids. In addition, because we studied nonsurgical patients, it is difficult to directly extrapolate our findings to the postoperative period with absolute confidence. Finally, we studied subjects with moderate OSA and administered a moderate opioid dose; more severe OSA and/or larger opioid doses may produce different results.

That said, our study does provide the first data characterizing opioid effects in OSA, and the findings give some cause for concern when prescribing opioids for these patients. In particular, the marked increase in number of central apneas experienced by a subset of patients is worrisome. Also concerning is the fact that we were unable to identify any reliable clinical indicators of which OSA patients are at risk for this particular opioid effect. Those factors we were able to identify as possibly associated with central apneas (increased age, lower BMI) are neither sufficiently sensitive nor specific to be effective screening tools. In fact, the possible inverse relationship with BMI is antithetical to the emphasis placed on obesity as a perioperative screening tool to identify patients at risk of having undiagnosed OSA. Clearly additional studies are necessary before we can clarify which OSA patients are at risk of harm from opioids in the perioperative period, and how best to prevent that harm. Until then, these data would suggest that caution be exercised in prescribing opioids, in deciding on patient disposition postoperatively, and in choosing monitoring postoperatively.

References

1. Kanagala R, Murali NS, Friedman PA, Ammash NM, Gersh BJ, Ballman KV, Shamsuzzaman AS, Somers VK: Obstructive sleep apnea and the recurrence of atrial fibrillation. Circulation 2003; 107:2589–94

2. Parish JM, Somers VK: Obstructive sleep apnea and cardiovascular disease. Mayo Clin Proc 2004; 79:1036–46

3. Peker Y, Hedner J, Norum J, Kraiczi H, Carlson J: Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: A 7-year follow-up. Am J Respir Crit Care Med 2002; 166:159–65

4. Shamsuzzaman AS, Gersh BJ, Somers VK: Obstructive sleep apnea: Implications for cardiac and vascular disease. Jama 2003; 290:1906–14

5. Sanders M, Givelber R: Overview of Obstructive Sleep Apnea in Adults, Sleep: A Comprehensive Handbook. Edited by Lee-Chiong T. Hoboken, John Wiley & Sons, 2006, pp 231–40

6. Robinson RW, Zwillich CW, Bixler EO, Cadieux RJ, Kales A, White DP: Effects of oral narcotics on sleep-disordered breathing in healthy adults. Chest 1987; 91:197–203

7. Benumof JL: Obesity, sleep apnea, the airway and anesthesia. Curr Opin Anaesthesiol 2004; 17:21–30

8. Boushra NN: Anaesthetic management of patients with sleep apnoea syndrome. Can J Anaesth 1996; 43:599–616

9. Connolly LA: Anesthetic management of obstructive sleep apnea patients. J Clin Anesth 1991; 3:461–9

10. Gross JB, Bachenberg KL, Benumof JL, Caplan RA, Connis RT, Cote CJ, Nickinovich DG, Prachand V, Ward DS, Weaver EM, Ydens L, Yu S: Practice guidelines for the perioperative management of patients with obstructive sleep apnea: A report by the American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. ANESTHESIOLOGY 2006; 104:1081–93

11. Meoli AL, Rosen CL, Kristo D, Kohrman M, Gooneratne N, Aguillard RN, Fayle R, Troell R, Kramer R, Casey KR, Coleman J Jr: Upper airway management of the adult patient with obstructive sleep apnea in the perioperative period—avoiding complications. Sleep 2003; 26:1060–5

12. Hume R: Prediction of lean body mass from height and weight. J Clin Pathol 1966; 19:389–91

13. Rechtschaffen A, Kales S: A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages in Human Subjects. Los Angeles, Brain Information Services/Brain Res Institute, University of California, 1968

14. EEG arousals: Scoring rules and examples: A preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep 1992; 15: 173-84

15. Egan TD, Huizinga B, Gupta SK, Jaarsma RL, Sperry RJ, Yee JB, Muir KT: Remifentanil pharmacokinetics in obese *versus* lean patients. ANESTHESIOLOGY 1998; 89:562–73

16. Egan TD, Minto CF, Hermann DJ, Barr J, Muir KT, Shafer SL: Remifentanil *versus* alfentanil: Comparative pharmacokinetics and pharmacodynamics in healthy adult male volunteers. ANESTHESIOLOGY 1996; 84:821–33

17. Westmoreland CL, Hoke JF, Sebel PS, Hug CC Jr, Muir KT: Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. ANESTHESIOLOGY 1993; 79:893–903

18. Bowdle TA, Camporesi EM, Maysick L, Hogue CW, Jr., Miguel RV, Pitts M, Streisand JB: A multicenter evaluation of remifentanil for early postoperative analgesia. Anesth Analg 1996; 83:1292–7

19. Yarmush J, D'Angelo R, Kirkhart B, O'Leary C, Pitts MC 2nd, Graf G, Sebel P, Watkins WD, Miguel R, Streisand J, Maysick LK, Vujic D: A comparison of remifentanil and morphine sulfate for acute postoperative analgesia after total intravenous anesthesia with remifentanil and propofol. ANESTHESIOLOGY 1997; 87:235–43

20. Kay DC, Eisenstein RB, Jasinski DR: Morphine effects on human REM state, waking state and NREM sleep. Psychopharmacologia 1969; 14:404–16

21. Shaw IR, Lavigne G, Mayer P, Choiniere M: Acute intravenous administration of morphine perturbs sleep architecture in healthy pain-free young adults: A preliminary study. Sleep 2005; 28:677–82

22. Dempsey JA, Smith CA, Harms CA, Chow C, Saupe KW: Sleep-induced breathing instability. University of Wisconsin-Madison Sleep and respiration Research Group. Sleep 1996; 19:236–47

23. Horner RL: Respiratory motor activity: Influence of neuromodulators and implications for sleep disordered breathing. Can J Physiol Pharmacol 2007; 85:155–65

24. Endo T, Roth C, Landolt HP, Werth E, Aeschbach D, Achermann P, Borbely AA: Selective REM sleep deprivation in humans: Effects on sleep and sleep EEG. Am J Physiol 1998; 274:R1186–94

25. Wang D, Teichtahl H: Opioids, sleep architecture and sleep-disordered breathing. Sleep Med Rev 2007; 11:35–46

26. Cepeda MS, Farrar JT, Baumgarten M, Boston R, Carr DB, Strom BL: Side effects of opioids during short-term administration: Effect of age, gender, and race. Clin Pharmacol Ther 2003; 74:102–12

27. Taylor S, Kirton OC, Staff I, Kozol RA: Postoperative day one: A high risk period for respiratory events. Am J Surg 2005; 190:752–6

28. Walker JM, Farney RJ, Rhondeau SM, Boyle KM, Valentine K, Cloward TV, Shilling KC: 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

29. Lehman S, Antic NA, Thompson C, Catcheside PG, Mercer J, McEvoy RD: Central sleep apnea on commencement of continuous positive airway pressure in patients with a primary diagnosis of obstructive sleep apnea-hypopnea. J Clin Sleep Med 2007; 3:462–6

30. Morgenthaler TI, Kagramanov V, Hanak V, Decker PA: Complex sleep apnea syndrome: Is it a unique clinical syndrome? Sleep 2006; 29:1203–9

31. Pusalavidyasagar SS, Olson EJ, Gay PC, Morgenthaler TI: Treatment of complex sleep apnea syndrome: A retrospective comparative review. Sleep Med 2006; 7:474–9

32. Moote CA, Knill RL: Isoflurane anesthesia causes a transient alteration in nocturnal sleep. ANESTHESIOLOGY 1988; 69:327–31

33. Rosenberg-Adamsen S, Skarbye M, Wildschiodtz G, Kehlet H, Rosenberg J: Sleep after laparoscopic cholecystectomy. Br J Anaesth 1996; 77:572–5