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Clinical Investigation

RESPIRATION AND THE AIRWAY

Opioid sensitivity in treated and untreated obstructive sleep apnoea: a prospective cohort study

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Abstract

Background: Opioid administration to patients with obstructive sleep apnoea (OSA) is controversial because they are believed to be more sensitive to opioids. However, objective data on opioid effects in OSA are lacking. We tested the hypothesis that subjects with untreated OSA have increased sensitivity to opioids compared with subjects without OSA, or with OSA treated with continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BIPAP).
Methods: This was a single-centre, prospective cohort study in subjects without OSA (n=20), with untreated OSA (n=33), or with treated OSA (n=21). OSA diagnosis was verified using type III (in-home) polysomnography. Subjects received a stepped-dose remifentanil infusion (target effect-site concentrations of 0.5, 1, 2, 3, 4 ng ml^{-1}). Primary outcome was miosis (pupil area fractional change), the most sensitive opioid effect. Secondary outcomes were ventilatory rate, end-expired CO_2, sedation, and thermal analgesia.
Results: There were no differences in miosis between untreated OSA subjects (mean=0.51, 95% confidence interval [CI] 0.41–0.61) and subjects without OSA (mean=0.49, 95% CI 0.36–0.62) (mean difference=0.02, 95% CI −0.18 to 0.22); between treated OSA subjects (mean=0.56, 95% CI 0.43–0.68) and subjects without OSA (difference=0.07, 95% CI −0.16 to 0.29); or between untreated OSA and treated OSA (difference=−0.05, 95% CI −0.25 to 0.16). There were no significant differences between subjects without OSA, untreated OSA, and treated OSA in ventilatory rate, end-expired CO_2, sedation, or thermal analgesia responses to remifentanil. There was no relationship between OSA severity and magnitude of opioid effects.
Conclusions: Neither obstructive sleep apnoea nor obstructive sleep apnoea treatment affected sensitivity to the miotic, sedative, analgesic, or respiratory depressant effects of the opioid remifentanil in awake adults. These results challenge conventional notions of opioid effects in obstructive sleep apnoea.
Clinical trial registration: NCT02898792 (clinicaltrials.gov).

Keywords: obstructive sleep apnoea; opioid sensitivity; remifentanil; respiratory depression; thermal pain

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Editor's key points

- Patients with obstructive sleep apnoea (OSA) are considered more sensitive to opioids, however objective data are lacking.
- In this prospective cohort study, opioid effects were analysed in subjects without OSA, with untreated OSA, or with treated OSA in response to escalating doses of remifentanil.
- There were no differences between groups in their sensitivities to the miotic, sedative, analgesic, or respiratory depressant effects of the opioid remifentanil in awake adults.
- These findings do not support the conventional concept of increased opioid sensitivity in OSA.
- The analgesic needs and treatment of patients with and without obstructive sleep apnoea should be considered in this context.

Opioid use in patients with obstructive sleep apnoea (OSA) is controversial. It is perceived as a conflicted choice between providing adequate pain relief and risking opioid-related toxicity. Pain is epidemic: 100 million Americans suffer pain.[1] Although adequate pain treatment is considered a fundamental right, pain is often undertreated.[2] Thus 80% of patients complain of inadequately treated postoperative pain, and 10–50% of surgical patients develop chronic pain, possibly as a result of inadequately treated postoperative pain.[3] Opioids are one of the few classes of systemic analgesics which reliably treat severe pain, but they can cause respiratory depression, and postoperative respiratory depression occurs in up to 17% of patients.[4,5]

OSA is the most common form of sleep-disordered breathing, afflicting at least 25 million Americans. Ten percent of adults have diagnosed OSA; an estimated 25% have undiagnosed OSA. The incidence is greater in obesity, which is epidemic.[6,7] In the USA, an estimated 2 million patients with known OSA will undergo surgery and need analgesia annually.[8,9]

It is conventionally accepted that adults with OSA have increased opioid sensitivity, and are at increased risk of opioid adverse effects, particularly respiratory depression.[4,5,7] Reviews and practice guidelines warn against, or even advocate avoiding, opioids in patients with OSA.[7] Nevertheless, objective evidence to support reducing or abandoning opioids in patients with OSA is sparse. Limited current evidence does not support a relationship between an isolated preoperative diagnosis of OSA and increased risk for postoperative opioid-induced ventilatory impairment.[10] OSA severity is heterogeneous. The degree that severity influences any altered opioid sensitivity is unknown.[11,12] Although the gold standard OSA treatment, continuous positive airway pressure (CPAP), ameliorates hypoxaemia and its associated morbidities, it is unknown whether CPAP also reverses the (purported) OSA increase in opioid sensitivity. Practice guidelines do not address whether CPAP-treated patients with OSA should be considered at-risk for opioid-induced respiratory depression.[7] An unmet need is objective data on the influence of OSA, both treated and untreated, on opioid responses.

We tested the impression that adults with untreated OSA have increased sensitivity to opioid effects, especially miosis, analgesia, and ventilatory depression. We also assessed the effects of CPAP on this sensitivity. Using the short-acting i.v. opioid remifentanil, we tested the hypotheses that (a) untreated OSA increases the miotic, analgesic, ventilatory, and sedative effects of remifentanil, (b) the increase is proportional to OSA severity (degree of night-time hypoxaemia), and (c) CPAP treatment of OSA normalises any altered remifentanil responses.

Methods

This study was approved by the Washington University in St. Louis Institutional Review Board on May 15, 2016, and was registered at Clinicaltrials.gov (NCT02898792) on September 13, 2016. The study was conducted between September 16, 2016 and May 16, 2018. Eligible subjects were volunteers 18–70 yr old. Exclusion criteria were: a history of liver disease, pregnant or nursing females, history of addiction to drugs or alcohol, craniofacial anomalies that precluded proper fit of pupillometry goggles, eye abnormalities that prevented measurement of pupil diameter, and use of home oxygen therapy. All subjects provided written informed consent.

During a pre-study subject screening visit, subjects completed a health self-assessment, pupillometry goggle fit testing, and were given instructions for polysomnography. Subjects were trained for thermal analgesia testing, which was assessed using a US Food and Drug Administration (FDA)-approved computer-controlled Peltier-type thermal stimulator (Pathway; Medoc, Ramat Yishai, Israel) applied to the forearm.[13,14] Heating started at 32°C and increased 0.5°C s^{-1} until the subject pressed a button indicating their maximum tolerated temperature. This was repeated three times, with the probe moved and cooled between stimuli. Results were the mean of the three temperatures. Subjects who reached the safety cut-off threshold (52°C) two or more times were not enrolled.

All subjects who completed screening had an at-home type III polysomnogram[15,16] in their normal sleeping location with a portable sleep apnoea monitor (Nox-T3; Carefusion, San Diego, CA, USA) within 1 month of the remifentanil infusion and assessments. Activity, heart rate, air flow, respiratory effort, and blood oxygenation were measured. Apnoea–hypopnoea index (AHI), average and nadir oxygen saturation, and OSA severity were calculated. Sleep studies were interpreted by a licensed sleep scientist (MM). OSA severity was defined according to the American Academy of Sleep Medicine manual for scoring sleep and associated events: absent (AHI <5), mild (AHI 5 to <15), moderate (AHI 15 to <30), or severe (AHI >30).[15,16] Subjects currently treated with CPAP used it at their prescribed settings. Subjects who provided data insufficient for interpretation from their first sleep study received repeat instructions and attempted the study again. Subjects whose data were not interpretable from a second sleep study were withdrawn.

The final study included three cohorts defined by polysomnography: (1) subjects without OSA, (2) subjects with untreated OSA (mild, moderate, or severe), who did not use CPAP or bilevel positive airway pressure (BIPAP), and (3) subjects with treated OSA, who had physician-diagnosed OSA and used CPAP or BIPAP per US Medicare guidelines (self-reported ≥4 h per night for ≥70% of nights slept). All subjects who used CPAP or BIPAP therapy used their device during polysomnography.

The remifentanil infusion portion of the study was conducted in the Washington University Clinical Trials Research Unit. Two 20G peripheral i.v. catheters were placed in opposite

arms for blood sampling and remifentanil administration. Monitors for continuous pulse oximetry, end-expired CO_2 ($eeCO_2$) ventilatory rate, heart rate, and EKG were placed. Noninvasive blood pressure was assessed before each blood draw. Ventilatory rate and end-expired CO_2 were monitored using a combined nasal-lip cannula via a Capnostream 20 Bedside Monitor (Medtronic, Minneapolis, MN, USA). Dark-adapted infrared pupillometry was performed using binocular infrared pupilometers mounted in light occlusive goggles sampling at 100 Hz (I-Portal; Neuro Kinetics, Inc., Pittsburg, PA, USA). Pupil area in pixels was obtained for 90 s before each blood draw. Data from both eyes were averaged.

A target-controlled stepped-dose remifentanil infusion was administered (programmed to achieve brain concentrations of 0.5, 1, 2, 3, or 4 ng ml^{-1} for 12 min at each concentration before obtaining measurements), using a computer-controlled syringe pump (Harvard-22; Harvard Apparatus, Cambridge, MA, USA). The syringe pump was controlled by Rugloop© software using the Minto Model for remifentanil pharmacokinetics.[17,18] Target-controlled infusion administers i.v. medications to obtain a predicted ('target') drug concentration.[19] Remifentanil dosing used ideal body weight.[20] At 12 min after each change in target plasma concentration, pupil area, ventilatory rate, end-expired CO_2, O_2 saturation, sedation (Modified Ramsay Sedation Scale, MRSS),[21] and response to thermal stimulus were recorded, in that order. A venous blood sample was obtained immediately before the thermal stimulus. Data collection and blood sampling took ~8 min at each remifentanil concentration. Each concentration epoch lasted ~20 min.

After the last analgesia assessment, the remifentanil infusion was stopped. During recovery and remifentanil washout, venous blood was sampled at 0, 2, 5, 10, 15, 30, 60, and 90 min, with citrate added to prevent remifentanil degradation. Plasma was stored at −80°C for subsequent determination of remifentanil concentration.[22] Upon cessation of the remifentanil infusion the pupillometry goggles were removed for participant comfort and pupil size was not measured further.

Statistical analyses

Sample Size Calculation: Estimating sample size for detecting a large effect (f=0.4) using a one-way analysis of variance (ANOVA) with alpha of 0.05 and 80% power yielded a minimum of 63 participants, 21 across three groups.[23] Sample size estimation was based on an expected 30% inter-individual variability, considered clinically significant. Using ANOVA, 20 subjects per group were determined to be necessary to detect a 30% difference in opioid response (α=0.05, 80% power).

A priori analyses included baseline characterisation of study cohorts and main outcomes by study cohorts. *Post hoc* analyses included longitudinal modelling. Univariate summary statistics (mean, standard deviation [SD]) were created for study cohorts, demographic and clinical background variables, and clinical measurements and outcomes to assess distribution. Results are grouped by the post-sleep study diagnosis. Categorical variables were compared using χ^2 tests, including by strata; Fisher's exact tests were used when expected cell sizes of comparisons were <5. Continuous variables were compared by categorical study group using non-parametric Kruskal–Wallis H tests since parametric assumptions were not upheld. Statistical significance was assigned at P<0.05 in two-sided tests. When overall differences were observed, *post hoc* tests applied a Bonferroni correction to mitigate type I error during three pairwise group comparisons to lower the threshold for statistical significance to P<0.0167 (0.05/3). Effect size for pairwise comparisons were estimated with Cohen's r.

Clinical outcomes were separately assessed longitudinally using a series of linear mixed-effect models for repeated measures with autoregressive correlation and restricted maximum likelihood estimation. For primary and secondary analyses of outcomes by study cohort, linear mixed-effect models used study cohort as a fixed effect with nominal procedure time as a repeated effect. Results are presented as estimated marginal means of study cohorts with pairwise differences adjusted for multiple comparisons via Bonferroni. For tertiary analyses of SpO_2 nadir association with each outcome, linear mixed-effect models used study cohort and SpO_2 nadir as fixed effects with nominal procedure time as a repeated effect. *Results are presented as the adjusted* linear mixed-effect models *for fixed effect of SpO2 nadir coefficients with 95% confidence intervals (CIs)*. Statistical analysis was performed using IBM SPSS Statistics for Mac (IBM, Armonk, NY, USA).

Results

Subject characteristics and sleep study characteristics

We screened 91 subjects between September 2016 and June 2018, and enrolled 84 of whom 82 successfully completed a sleep study. Seventy-five subjects participated in the remifentanil infusion and 74 completed the infusion (Fig. 1). The final cohorts were participants with normal sleep studies (n=20), those with sleep studies indicating at least mild OSA (n=33), and those with self-reported OSA who were compliant with CPAP or BIPAP therapy (n=21) (Tables 1 and 2). No attempt was made to match groups for demographic variables. Self

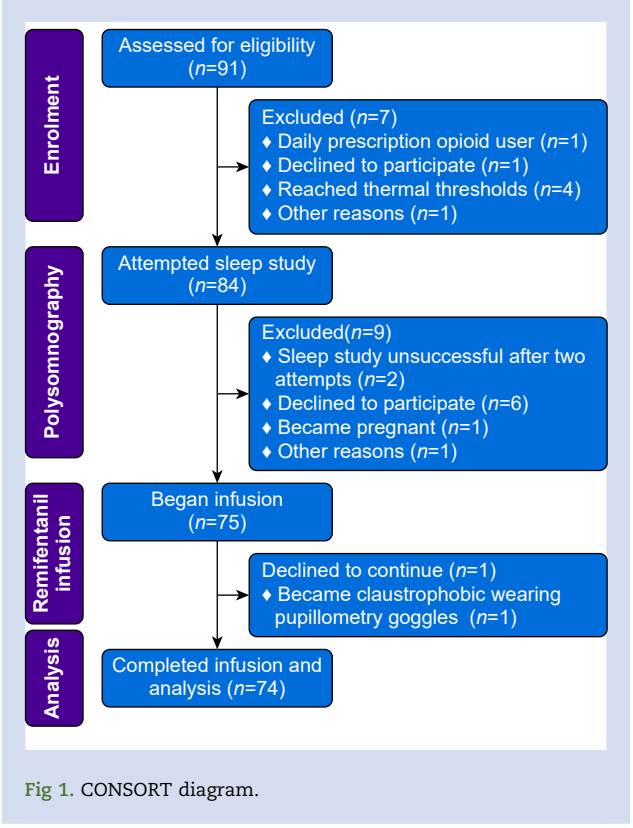

Fig 1. CONSORT diagram.

Table 1 Subject cohorts based on polysomnography. BIPAP, bilevel positive airway pressure; OSA, obstructive sleep apnoea. Mean (standard deviation).

Characteristic	Study cohort		
	Without OSA, n=20	OSA untreated, n=33	CPAP/BIPAP-treated OSA, n=21
Sex, male, no. (%)	5 (25)	12 (36)	7 (33)
Age (yr) (range)	42 (24–62)	55 (33–70)	53 (30–70)
Weight (kg)	70 (8)	92 (27)	109 (13)
BMI	26 (3)	32 (9)	34 (9)
Apnoea-hypopnea index	2 (1)	25 (22)	3 (3)
SpO_2 nadir	91 (2)	81 (7)	88 (5)
SpO_2 average (%)	96 (1)	94 (2)	96 (1)
Serum bicarbonate (mEq L^{-1})	26 (3)	27 (2)	26 (2)
Baseline pupil area (pixels)	5812 (1856)	4925 (1573)	5746 (2103)

Table 2 Difference between pre-study self-report and polysomnography diagnosis (n=74). OSA, obstructive sleep apnoea.

Pre-study self-report	Polysomnography diagnosis, n (%)			P-value
	Without OSA n=20	CPAP-treated OSA n=21	Untreated OSA n=33	
Without OSA, n=32	18 (56)	0 (0)	14 (44)	0.003
OSA untreated, n=21	2 (10)	0 (0)	19 (91)	
OSA treated, n=21	0 (0)	21 (100)	0 (0)	

report was only 100% consistent with polysomnography diagnosis in patients with CPAP/BIPAP treated OSA.

Pharmacologic and clinical effects

Miosis

Remifentanil dose-dependently decreased pupil area in all participants, with maximal decrease at 3 ng ml^{-1} or greater (Fig. 2a). Miosis (fractional pupil change) between untreated OSA subjects (mean=0.51, 95% CI 0.41–0.61) and subjects without OSA (mean=0.49, 95% CI 0.36–0.62) was not different in the adjusted linear mixed-effects model (mean difference=0.02, 95% CI −0.18 to 0.22). Miosis of OSA-treated subjects (mean=0.56, 95% CI 0.43–0.68) did not differ from subjects without OSA in the adjusted linear model (mean difference=0.07, 95% CI −0.16 to 0.29). Miosis of untreated OSA subjects did not differ from treated OSA subjects in the adjusted linear model (mean difference=−0.05, 95% CI −0.25 to 0.16).

Analgesia

Remifentanil (Fig. 2b) dose-dependently increased tolerance to a heat stimulus in all participants. Remifentanil-induced thermal analgesia (estimated marginal mean maximum tolerated temperature) between subjects with untreated OSA (mean=49°C, 95% CI 48–50°C) and subjects without OSA (mean=48°C, 95% CI 47–49°C) was not different in the adjusted linear mixed model (LMM; mean difference=0.74°C, 95% CI −0.75 to 2.23°C). Remifentanil-induced thermal analgesia in subjects with treated OSA (mean=49°C, 95% CI 48–50°C) did not differ from subjects without OSA in the adjusted linear model (mean difference=0.71°C, 95% CI −0.93 to 2.34°C). Remifentanil-induced thermal analgesia in subjects with untreated OSA did not differ from subjects with treated OSA in the adjusted linear model (mean difference=0.04°C, 95% CI −1.43 to 1.50°C).

End-expired CO_2

Remifentanil increased end-expired CO_2 in all participants (Fig. 3a). Remifentanil-induced end-expired CO_2 changes between subjects with untreated OSA (estimated marginal mean=5.47 kPa, 95% CI 5.33–6.00 kPa [mean=41 mm Hg, 95% CI 40–42 mm Hg]) and subjects without OSA (mean=5.33 kPa, 95% CI 5.20–6.00 kPa [mean=40 mm Hg, 95% CI 39–42 mm Hg]) were not different in the adjusted linear model (mean difference=1.1, 95% CI −1.2 to 3.5). End-expired CO_2 of subjects with treated OSA (mean=5.47 kPa, 95% CI 5.33–5.73 kPa [mean=41 mm Hg, 95% CI 40–43 mm Hg]) did not differ from subjects without OSA in the adjusted linear model (mean difference=1.2, 95% CI −1.4 to 3.8). End-expired CO_2 in subjects with untreated OSA did not differ from subjects with treated OSA in the adjusted linear model (mean difference=−0.1, 95% CI −2.4 to 2.3).

Ventilatory rate

Remifentanil caused a dose-dependent decrease in ventilatory rate in all participants (Fig. 3b). Estimated marginal ventilatory rates between subjects with untreated OSA (mean=15, 95% CI 14–16) and subjects without OSA (mean=14, 95% CI 13–16) was not different in the adjusted linear model (mean difference=0.6, 95% CI −1.2 to 2.5). Ventilatory rates of subjects with treated OSA (mean=15, 95% CI 14–17) did not differ from subjects without OSA in the adjusted linear model (mean difference=1.5, 95% CI −0.6 to 3.5). Ventilatory rates of subjects with untreated OSA did not differ from subjects with treated OSA in the adjusted linear model (mean difference=−0.8, 95% CI −2.6 to 1.0).

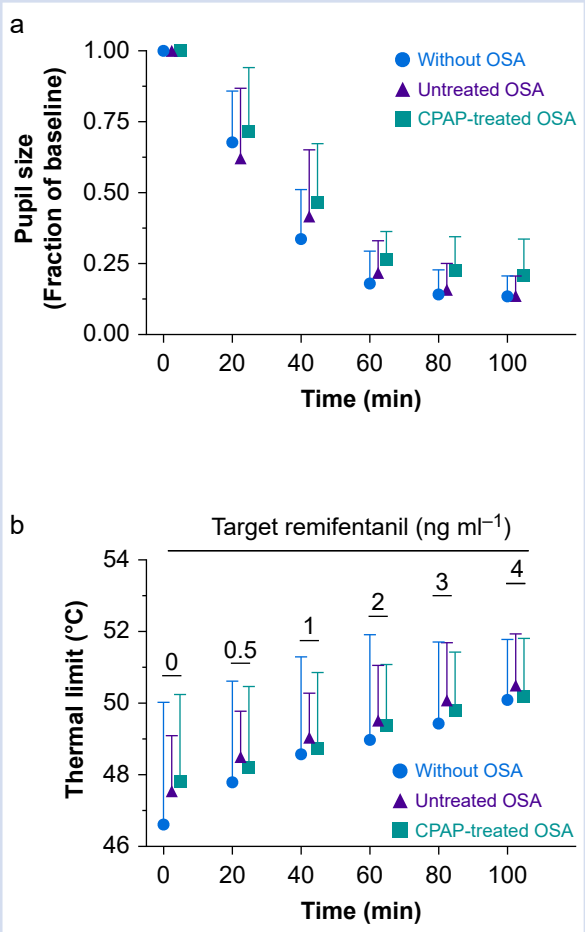

Fig 2. Opioid (remifentanil) effects on (a) pupil size and (b) thermal analgesia in participants without obstructive sleep apnoea (n=20), with untreated obstructive sleep apnoea (n= 33), and with CPAP or BIPAP-treated obstructive sleep apnoea (n=21). Results are mean (standard deviation). BIPAP, bilevel positive airway pressure; OSA, obstructive sleep apnoea.

Sedation

Remifentanil caused dose-dependent sedation (Fig. 3c). Remifentanil-induced sedation between subjects with untreated OSA (mean=1, 95% CI 1–1) and subjects without OSA (mean=1, 95% CI 1–1) was not different in the adjusted linear model (mean difference=0.1, 95% CI −0.1 to 0.2). Remifentanil-induced sedation of subjects with treated OSA (mean=1, 95% CI 1–1) did not differ from subjects without OSA in the adjusted linear model (mean difference=0.1, 95% CI −0.2 to 0.3). Remifentanil-induced sedation of subjects with untreated OSA did not differ from subjects with treated OSA in the adjusted linear model (mean difference=0.0, 95% CI −0.2 to 0.2).

Oxygen saturation nadir and pharmacologic and clinical effects

Relationships between OSA severity as measured by SpO_2 nadir and remifentanil effects were assessed. No differences between groups were found in remifentanil miosis or

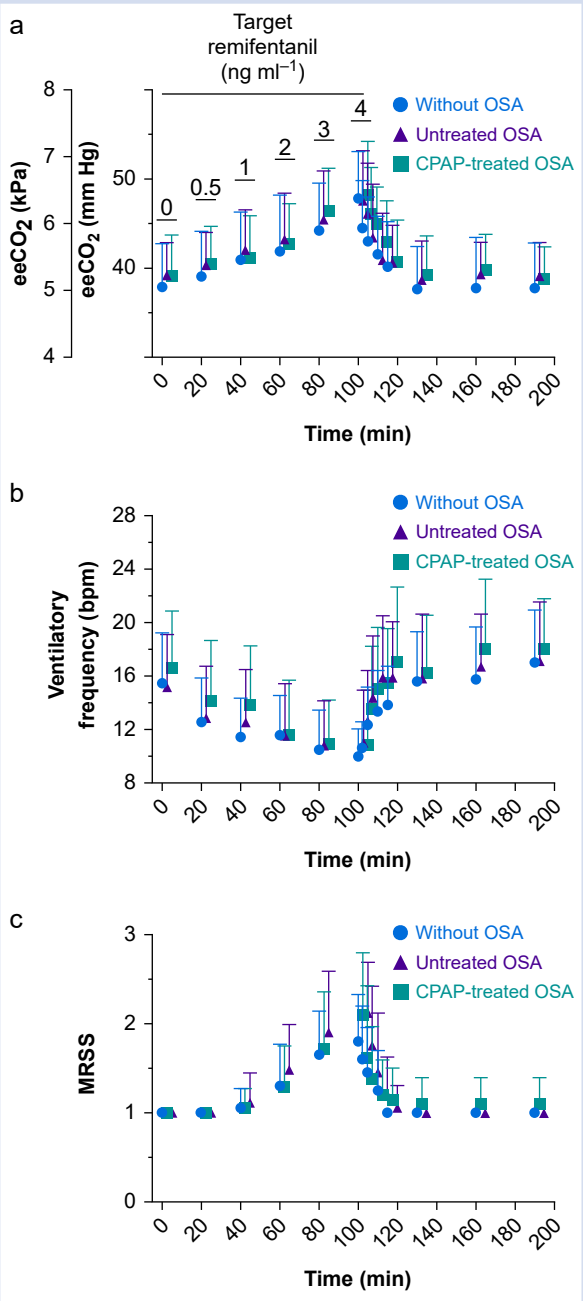

Fig 3. Opioid (remifentanil) effects on ventilatory parameters: (a) average end-expired CO_2 ($eeCO_2$); (b) ventilatory rate, and on sedation. (c) Modified Ramsay Sedation Scale (MRSS) in participants without obstructive sleep apnoea (n=20), with untreated obstructive sleep apnoea (n=33), and with CPAP or BIPAP-treated obstructive sleep apnoea (n=21). Results are mean (standard deviation). MRSS ranges from 0 to 6 with 0=paralysed, unable to evaluate; 1=awake; 2=lightly sedated; 3=moderately sedated, follows simple commands; 4=deeply sedated, responds to non-painful stimuli; 5=deeply sedated, responds only to painful stimuli; and 6=deeply sedated, unresponsive to painful stimuli. BIPAP, bilevel positive airway pressure; OSA, obstructive sleep apnoea.

ventilatory effects (Fig. 4). In the adjusted linear model, neither miosis (β=−0.005, 95% CI −0.014 to 0.004), ventilatory rate (β=−0.05, 95% CI −0.20 to 0.10) nor end-expired CO_2 were associated with OSA severity (SpO_2 nadir).

Adverse events

There were 94 adverse events, with no serious adverse events. All adverse events were expected, based on the known pharmacology of remifentanil. In rank order of occurrence, adverse events were nausea (28 participants), itching (20), respiratory depression defined as a ventilatory rate <8 min^{-1} (14), emesis (11), dizziness (eight), and oxygen saturation <90% for >1 min (five). Eight participants experienced other adverse events (e.g. bradycardia with i.v. catheter placement). There were no differences in adverse event rates between the three groups (χ^2 test or Fisher's exact test, all *P*-values ≥0.2).

Discussion

We assessed opioid sensitivity to the short-acting i.v. opioid remifentanil in awake adults without OSA, adults with untreated OSA, and adults with OSA treated with CPAP or BIPAP, using objective clinical measurement. Based on published review articles, practice guidelines, and conventional thought, we expected greater remifentanil clinical effects in subjects with untreated OSA compared with subjects without OSA.[7,24] However, there were no differences in the primary outcome, remifentanil-induced miosis, between participants without OSA and untreated OSA, or between participants without OSA and treated OSA. Similarly, there were no differences in any of the secondary outcomes (thermal analgesia, ventilatory rate, end-expired CO_2, sedation) between participants without OSA and untreated OSA, or between participants without OSA and treated OSA. Furthermore, there was no relationship between the severity of OSA and the magnitude of remifentanil-induced ventilatory or sedative effects, nor any other secondary outcome. These results refute the hypotheses that OSA increases the miotic, analgesic, ventilatory, and sedative effects of remifentanil, that such opioid sensitivity is proportional to OSA severity (degree of nighttime hypoxaemia), and CPAP or BIPAP treatment of OSA normalises any altered remifentanil responses.

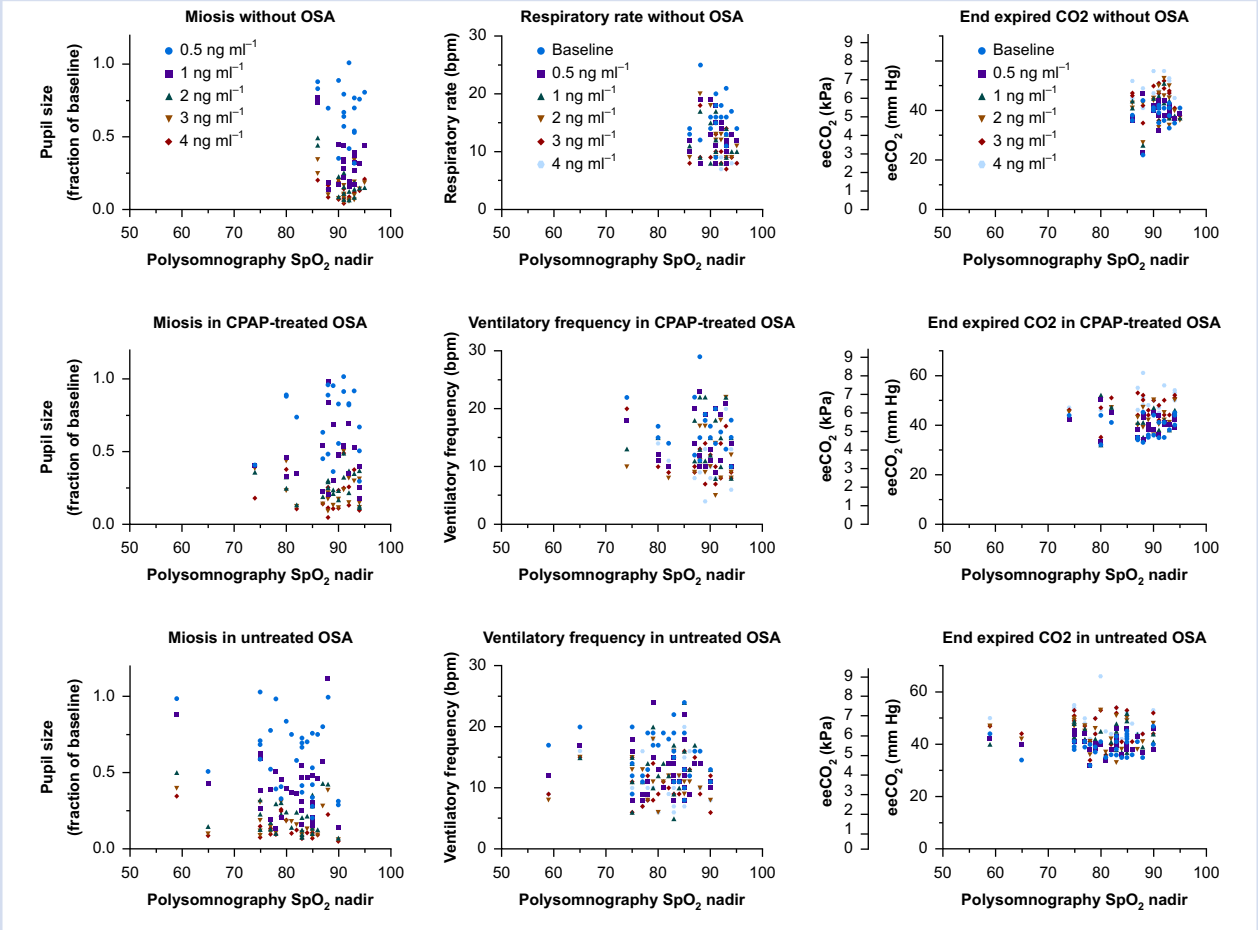

Fig 4. Relationship between obstructive sleep apnoea severity as measured by SpO_2 nadir and remifentanil effects. Subjects are categorised by obstructive sleep apnoea diagnosis as 'Without OSA' (first column), 'untreated OSA' (second column), and 'with CPAP-treated OSA' (third column). The target effect-site concentration for each opioid-induced effect is colour and symbol coded. The SpO_2 nadir obtained by polysomnography is on the x-axis. The y-axes are opioid effects: pupil size (first row), ventilatory rate (second row), and end-expired CO_2 (third row). OSA, obstructive sleep apnoea.

Remifentanil was used as a representative μ-opioid agonist because of its fast onset, fast blood–brain equilibration, and rapid elimination, allowing drug infusions to rapidly achieve and maintain target concentrations, ensuring that measured effects were at the steady-state target dose. Remifentanil effects in general are described by separate and parallel concentration–response curves for miosis, analgesia, respiratory depression, and sedation, and most piperidine opioids are similar in effects albeit with different concentration–effect curves. Miosis and sedation occur at the lowest and highest concentrations, respectively. The most clinically relevant effects we measured were analgesia and respiratory depression. Miosis is the most sensitive effect. Analgesia is a particularly good model for remifentanil pharmacodynamics.

Previous studies have not shown a link between OSA and greater opioid-induced ventilatory effects. In volunteers with moderate OSA, a parallel group study of remifentanil infusion *vs* placebo infusion during night-time sleep found that the number of obstructive apnoeas was significantly lower in the remifentanil group, although the number of central apnoeas was greater.[25] In a crossover study of volunteers with moderately severe OSA who received morphine or placebo before night-time sleep, there were no differences between groups in airway collapsibility (pharyngeal critical closure pressure), pharyngeal muscle responsiveness, respiratory arousal threshold, or ventilatory control during sleep, although ventilatory control was altered consistent with blunted chemosensitivity. In a study of volunteers with moderately severe OSA who received morphine or placebo before night-time sleep, there was no difference between groups in the AHI. In awake surgical patients with moderate-to-severe OSA, compared with healthy surgical patients, all given a brief remifentanil infusion, effects on minute ventilation were not different between groups. In addition, OSA severity (apnoea/hypopnea events per hour of sleep or minimum nocturnal oxygen saturation) did not influence sensitivity to remifentanil ventilatory depression.[26] In awake children (8–14 yr old) given a fixed-rate remifentanil infusion, there was no difference between children with or without OSA in the remifentanil concentration–effect (miosis) relationship.[22] In patients undergoing hip arthroplasty, some of whom had OSA and some of whom received intrathecal morphine, there was no significant interaction between OSA and morphine on the outcome of AHA, suggesting that intrathecal morphine does not increase sleep apnoea severity. In a prospective study of 1218 patients undergoing major noncardiac surgery and the association between postoperative cardiovascular events and unrecognised OSA, there was no significant interaction between perioperative outcomes and use of supplemental opioids.[27] Taken together, our quantitative results and previous observations challenge the notion that patients with OSA are more sensitive to remifentanil. If remifentanil is representative of opioid effects more generally, these results question the assumption that adults with untreated OSA have increased sensitivity to opioids. Moreover, it might render moot the question of whether to consider OSA patients treated with CPAP or BIPAP to be more sensitive to opioids or to be normalised.

The reason for lack of greater remifentanil sensitivity in OSA patients is not apparent. There could be no difference. Alternatively, there could be counteracting influences on remifentanil pharmacokinetics and pharmacodynamics that would mask differences in both. Effect could depend on OSA phenotype.[28]

American Society of Anesthesiologists Guidelines state 'patients at increased perioperative risk from OSA are especially susceptible to the respiratory depressant and airway effects of opioids',[7] and 'some practitioners reduce or entirely avoid opioids in patients with OSA for fear of causing respiratory depression'.[29] If correct, patients with OSA could be at greater risk of opioid-related adverse effects, and opioid dosing should be reduced. However, if incorrect, unnecessarily reduced opioid use could expose patients to insufficiently treated pain, and opioids should not be automatically avoided in patients with OSA.

The number of people affected by the pain epidemic dwarfs the opioid crisis.[2] Opioids remain the most effective treatment for severe acute pain. Evidence for withholding opioids from patients with OSA is scant, and is now challenged by several studies, including this one. Furthermore, OSA is heterogeneous,[12] and polysomnography is not always performed before to surgery. Here, ~20% of subjects had a different polysomnogram diagnosis than self-report. Fourteen of 32 subjects who did not believe they had OSA were found to have at least mild OSA. Nearly 10% of those who had been told by a physician that they had OSA had a normal polysomnogram. The only group in which self-report was consistent was that with CPAP-treated OSA. Thus, opioid prescribing based on OSA self-report risks using an incorrect diagnosis.

This study has limitations. Selection bias is possible because participants were volunteers. Participants were awake while receiving an i.v. opioid infusion under direct physician supervision. Results might not be generalisable to outpatients not under direct observation, those receiving oral opioids in an unmonitored setting, or opioid effects during sleep. We studied one pain model, thermal pain tolerance. Other pain models (cold, pressure, electrical, and chemical stimulation) have also been used experimentally. It has been suggested that patients with OSA are at higher risk for opioid-induced respiratory depression while asleep or sedated than when awake. We enrolled a small number of participants and our study was neither designed to detect rare events nor robustly resist confounding effects. Remifentanil is a μ-opioid agonist; effects should be generalisable to other μ-opioids. However, its rapid equilibration and clearance is unusual, and these findings will need to be confirmed with other opioids. Opioid effects were tested in isolation without sedative-hypnotic drugs that are typically used in the perioperative period. Finally, while the endpoints we assessed (e.g. ventilatory rate and end-expired CO_2) are measures of ventilation, they do not directly measure the responsiveness of ventilatory control neural circuitry or chemoreflex loops that might be suppressed by exogenously administered opioids. Nevertheless, we did not identify a difference in sensitivity to opioid-induced respiratory depression, sedation, or analgesia related to a polysomnography-verified diagnosis of OSA.

In summary, obstructive sleep apnoea did not affect multiple metrics of remifentanil clinical effects in awake adults. Treatment of obstructive sleep apnoea with CPAP or BIPAP did not affect any metric of remifentanil effect in awake adults. The analgesic needs and pain treatment of patients with and without obstructive sleep apnoea should be considered in this context.

Authors' contributions

Declare accountability for all aspects of the work herein: all authors
Study conceptualisation and design: MCM, MM, EDK
Acquisition of data: MCM, MF, LJ
Analysis of data: all authors
Interpretation of data: MCM, MM, PME, EDK
Drafting the manuscript: MCM, PME, EDK
Critically revising the manuscript: MCM, MM, MF, LJ, EDK
Final approval of the submitted manuscript: all authors

Declaration of interest

The authors declare that they have no conflicts of interest.

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References

1. Institute of Medicine. *Relieving pain in America: a blueprint for transforming prevention, care, education, and Research*. Washington, DC: National Academies Press (US); 2011. PMID: 22553896
2. Skolnick P, Volkow ND. Re-energizing the development of pain therapeutics in light of the opioid epidemic. *Neuron* 2016; **92**: 294–7
3. Kharasch ED, Brunt LM. Perioperative opioids and public health. *Anesthesiology* 2016; **124**: 960–5
4. Lee LA, Caplan RA, Stephens LS, et al. Postoperative opioid-induced respiratory depression: a closed claims analysis. *Anesthesiology* 2015; **122**: 659–65
5. Chung F, Liao P, Elsaid H, Shapiro CM, Kang W. Factors associated with postoperative exacerbation of sleep-disordered breathing. *Anesthesiology* 2014; **120**: 299–311
6. Romero-Corral A, Caples SM, Lopez-Jimenez F, Somers VK. Interactions between obesity and obstructive sleep apnea: implications for treatment. *Chest* 2010; **137**: 711–9
7. American Society of Anesthesiologists Task. Force on Perioperative Management of patients with obstructive sleep apnea. Practice guidelines for the perioperative management of patients with obstructive sleep apnea: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. *Anesthesiology* 2014; **120**: 268–86
8. Hall MJ, Schwartzman A, Zhang J, Liu X. Ambulatory surgery data from hospitals and ambulatory surgery centers: United States, 2010. *Natl Health Stat Report* 2017; **1–15**
9. Steiner CA, Karaca Z, Moore BJ, Imshaug MC, Pickens G. *Surgeries in hospital-based ambulatory surgery and hospital inpatient settings, 2014: statistical brief #223. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs*. Rockville, Maryland: Agency for Healthcare Research and Quality (US); 2006. PMID: 28722845
10. Doufas AG. Obstructive sleep apnea, pain, and opioid analgesia in the postoperative patient. *Curr Anesthesiol Rep* 2014; **4**: 1–9
11. Mason M, Cates CJ, Smith I. Effects of opioid, hypnotic and sedating medications on sleep-disordered breathing in adults with obstructive sleep apnoea. *Cochrane Database Syst Rev* 2015; **7**: CD011090
12. Subramani Y, Singh M, Wong J, Kushida CA, Malhotra A, Chung F. Understanding phenotypes of obstructive sleep apnea: applications in anesthesia, surgery, and perioperative medicine. *Anesth Analg* 2017; **124**: 179–91
13. Meissner K, Blood J, Francis AM, Yermolenka V, Kharasch ED. Cyclosporine-inhibitable cerebral drug transport does not influence clinical methadone pharmacodynamics. *Anesthesiology* 2014; **121**: 1281–91
14. Meissner K, Avram MJ, Yermolenka V, Francis AM, Blood J, Kharasch ED. Cyclosporine-inhibitable blood-brain barrier drug transport influences clinical morphine pharmacodynamics. *Anesthesiology* 2013; **119**: 941–53
15. Berry RB, Brooks R, Gamaldo CE, Harding SM, Lloyd RM. *Vaughn BV for the American Academy of sleep medicine. The AASM Manual for the Scoring of Sleep and associated events: rules, Terminology and technical specifications*. 2. 2 Edn. Darien, Illinois: American Academy of Sleep Medicine; 2015
16. Collop NA, Anderson WM, Boehlecke B, et al. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2007; **3**: 737–47
17. Minto CF, Schnider TW, Egan TD, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. *Anesthesiology* 1997; **86**: 10–23
18. Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. *Anesthesiology* 1997; **86**: 24–33
19. Absalom AR, Glen JI, Zwart GJ, Schnider TW, Struys MM. Target-controlled infusion: a mature technology. *Anesth Analg* 2016; **122**: 70–8
20. Egan TD, Huizinga B, Gupta SK, et al. Remifentanil pharmacokinetics in obese versus lean patients. *Anesthesiology* 1998; **89**: 562–73
21. Barr J, Egan TD, Sandoval NF, et al. Propofol dosing regimens for ICU sedation based upon an integrated pharmacokinetic-pharmacodynamic model. *Anesthesiology* 2001; **95**: 324–33

22. Montana MC, Juriga L, Sharma A, Kharasch ED. Opioid sensitivity in children with and without obstructive sleep apnea. *Anesthesiology* 2019; **130**: 936–45
23. Cohen J. A power primer. *Psychol Bull* 1992; **112**: 155–9
24. Lam KK, Kunder S, Wong J, Doufas AG, Chung F. Obstructive sleep apnea, pain, and opioids: is the riddle solved? *Curr Opin Anaesthesiol* 2016; **29**: 134–40
25. Bernards CM, Knowlton SL, Schmidt DF, et al. Respiratory and sleep effects of remifentanil in volunteers with moderate obstructive sleep apnea. *Anesthesiology* 2009; **110**: 41–9
26. Doufas AG, Shafer SL, Rashid NHA, Kushida CA, Capasso R. Non-steady state modeling of the ventilatory depressant effect of remifentanil in awake patients experiencing moderate-to-severe obstructive sleep apnea. *Anesthesiology* 2019; **130**: 213–26
27. Chan MTV, Wang CY, Seet E, et al. Association of unrecognized obstructive sleep apnea with postoperative cardiovascular events in patients undergoing major noncardiac surgery. *JAMA* 2019; **321**: 1788–98
28. Freire C, Sennes LU, Polotsky VY. Opioids and obstructive sleep apnea. *J Clin Sleep Med* 2022; **18**: 647–52
29. Mulier JP. Perioperative opioids aggravate obstructive breathing in sleep apnea syndrome: mechanisms and alternative anesthesia strategies. *Curr Opin Anaesthesiol* 2016; **29**: 129–33

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