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Remifentanil Inhibits Rapid Eye Movement Sleep but Not the Nocturnal Melatonin Surge in Humans

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Background: **Postoperative patients are sleep deprived. Opioids, commonly administered for postoperative pain control, are often mistakenly considered inducers of naturally occurring sleep. This study describes the effect of the opioid remifentanil on nocturnal sleep in healthy volunteers. In addition, this study tests the hypothesis that opioid-induced sleep disturbance is caused by a circadian pacemaker disturbance, reflected by suppressed nocturnal plasma concentration of melatonin.**

Methods: **Polysomnography was performed in 10 volunteers from 11:00 PM to 7:00 AM for four nights at 6-day intervals. On two nights, remifentanil (0.01–0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused from 10:30 PM to 7:00 AM, and either a placebo capsule or 3.0 mg melatonin was administered at 10:30 PM. On two additional nights, saline was infused, and the placebo or melatonin capsules were administered at 10:30 PM. Blood was drawn at 12:00 AM, 3:00 AM, and 6:00 AM to measure the plasma concentration of melatonin and cortisol. A repeated-measures analysis of variance model was used to determine the effect of remifentanil on sleep stages, the effect of remifentanil on the plasma concentration of melatonin, and the effect of exogenous melatonin on remifentanil-induced sleep disturbance.**

Results: **Remifentanil inhibited rapid eye movement sleep (14.1 ± 7.2% to 3.9 ± 6.9%). The amount of slow wave sleep decreased from 6.8 ± 7.6% to 3.2 ± 6.1%, but this decrease was not statistically significant. Remifentanil did not decrease melatonin concentration. Melatonin administration did not prevent remifentanil-induced sleep disturbance.**

Conclusions: **An overnight constant infusion of remifentanil inhibits rapid eye movement sleep without suppressing the nocturnal melatonin surge.**

RESTFUL sleep is rare on the first night after surgery.[1–3] Pain disrupts sleep,[4–6] and opioids, which are a mainstay of surgical pain management, also inhibit sleep. The twofold purpose of this study was to describe the effect of a constant opioid infusion on nocturnal sleep in normal volunteers and to test the hypothesis that opioid-induced sleep disturbance is caused by disturbance of the circadian pacemaker.

Early studies in former opioid-dependent prisoners[7–11] and a recent study in opioid-naive healthy volunteers[12] demonstrated that morphine and other opioids dose-dependently inhibit sleep, especially slow wave sleep (SWS) and rapid eye movement (REM) sleep. In all of these studies, the dose of opioid was administered before the sleep recording period. Therefore, it remains unclear whether the sleep disturbance is caused by the presence of opioid or by the decrease in the opioid concentration, as is commonly seen in the agitation of withdrawal after chronic opioid use.[13] Development of a rapidly metabolized opioid, remifentanil, has made it possible to achieve a stable blood concentration of opioid by administering a constant intravenous infusion.[14] Therefore, we are able to study the opioid effect on nocturnal sleep without the possibly confounding effect of increasing and decreasing opioid blood concentrations throughout the night.

Some sleep disturbances, such as jet lag, result from relative derangement of the circadian pacemaker.[15] Postoperative patients demonstrate circadian rhythm disturbances not only in the sleep–wake cycle but also in other circadian rhythms, such as temperature,[16] and cortisol[17] and melatonin secretion.[18] The possible role opioids play in circadian pacemaker disturbance is undefined.

Cells in many tissues in mammals have circadian oscillators coordinated by a central pacemaker in the suprachiasmatic nuclei.[19] The function of the mammalian circadian pacemaker is to organize daily rhythms in behavior and physiology. Circadian (24 h) variations in neurons within the suprachiasmatic nuclei have been characterized using metabolic, histochemical, and electrophysiologic techniques.[20] Blood concentration of melatonin varies as a function of the 24-h day and provides a reliable marker of circadian rhythms.[21,22]

Melatonin is a hormone produced by the pineal gland under the control of the circadian pacemaker in the suprachiasmatic nuclei.[23] Normally, the melatonin concentration is low throughout the day, begins increasing in the evening to peak around 2:00 AM, and decreases to daylight levels by 8:00 AM. The nocturnal melatonin peak concentration is 5–10 times higher than the diurnal peak concentration. In addition to serving as a marker of the endogenous output of the circadian pacemaker, melatonin can be administered exogenously to manipulate or entrain the circadian pacemaker.[24,25] For example, nocturnal administration of melatonin to subjects with either suppressed or incorrect timing of the nocturnal melatonin peak[26] improves sleep quality and especially REM sleep duration.[27] Nocturnal melatonin suppression in intensive care unit patients and postoperative patients has been described,[28,29] but the effect of

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opioids on nocturnal secretion of melatonin has not been described.

This study tests the hypothesis that an overnight constant infusion of remifentanil inhibits both nocturnal REM sleep and melatonin secretion in normal humans, and that administration of exogenous melatonin during opioid administration will ameliorate the opioid-induced sleep disturbance.

Materials and Methods

After the Milton S. Hershey Institutional Review Board (Hershey, Pennsylvania) approved the study, 12 healthy volunteers providing written informed consent were enrolled. Eligibility requirements excluded subjects with any medical disorder, current use of any medications other than birth control pills, or a history of chronic or recent opioid use. Night shift workers and subjects with snoring, insomnia, or daytime somnolence were also excluded.

Experimental Design

Each subject spent four pairs of nights in the General Clinical Research Center at the Penn State Milton S. Hershey Medical Center (fig. 1). Each pair of General Clinical Research Center nights included an acclimation night followed by a data collection night, which was then followed by a rest interval of five consecutive nights at home. On the acclimation night, the subjects' experiences were identical to their experiences on the following data collection night, except that instead of having an intravenous catheter inserted, tubing for an intravenous infusion was taped to their arm. On the data collection night, subjects received one of the following four treatments: saline infusion plus placebo capsule (saline–placebo), remifentanil (Abbott Laboratories, Abbott Park, IL) infusion plus placebo capsule (remifentanil–placebo), saline infusion plus melatonin capsule (saline–melatonin), or remifentanil infusion plus melatonin capsule (remifentanil–melatonin). To enable exclusion of subjects who were unable to sleep in the study environment, all subjects received the saline–placebo treatment on the first data collection night. The order of the subsequent three treatments was randomized.

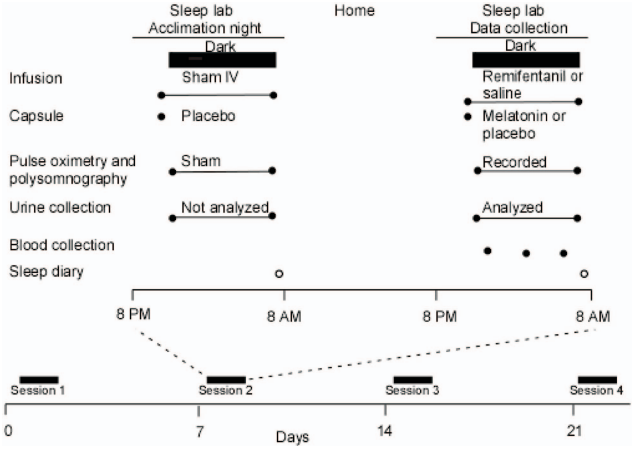

Fig. 1. Schema of study protocol. Each session included 36 h. During the first session, the infusion was always saline and the capsule was always placebo. In the subsequent three sessions, subjects received either remifentanil or saline and either melatonin or placebo.

During the daylight hours between the acclimation night and the data collection night, subjects were instructed to resume their normal activities and to avoid napping. They were asked to avoid alcohol entirely and to avoid chocolate and caffeine-containing beverages after 4:00 PM.

Remifentanil Titration

On the first night of the study, subjects were admitted to the General Clinical Research Center at 8:00 PM. An intravenous catheter was placed, and an infusion of saline at 80 ml/h was begun. Subjects rested supine and were observed while wearing a pulse oximeter in a lighted room. For minutes 20, 25, and 30 of observation, the subjects' respiratory rate and oxygen saturation were recorded and averaged to obtain a baseline value. An infusion of 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil was then begun, and the respiratory rate and oxygen saturation were recorded every 5 min. The remifentanil infusion was increased to 0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$ after 30 min, but if the respiratory rate became less than or equal to 75% of baseline or the oxygen saturation decreased 3% or more for two consecutive observations, the infusion rate was reduced in 0.01-$\mu g \cdot kg^{-1} \cdot min^{-1}$ increments and was observed for 30 min until the respiratory rate and oxygen saturation were greater than or equal to these thresholds. This titration was performed to achieve a definite but mild, uniform, and objective opioid physiologic effect.

Melatonin Capsule and Remifentanil Infusion

At 10:30 PM on the acclimation and data collection nights, a study capsule was administered to subjects. On the acclimation night, this was always a placebo. On the data collection nights, it was either a placebo or 3.0 mg melatonin. The otherwise identical melatonin (Helsinn Chemicals, SA, Biasca, Switzerland) and placebo capsules were compounded by a pharmacist (Suspenders Pharmacy, Hershey, PA). Both the subjects and the study personnel were blinded to this treatment allocation. On each data collection night, an intravenous catheter was placed in the proximal arm. At 10:30 PM, an infusion of saline at 80 ml/h or remifentanil at the predetermined rate (0.02–0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was initiated. The infusion was terminated at 7:00 AM the next morning. The intravenous tubing, used for both blood sampling and drug administration, ran under the door to a pump

located outside the room. The subjects, but not the study personnel, were blinded to the treatment order.

Sleep Monitoring

On the acclimation nights and treatment nights, cup electrodes with electrolyte paste were applied to the scalp and face for performing standard polysomnography. The wires were run under the door to the sleep recording equipment (Oxford Medilog Sleep Analysis Computer; Oxford Instruments, Clearwater, FL) outside the room. At 11:00 PM, the lights, radio, and television were turned off, the door was closed, and the recording period began. Subjects were left undisturbed until the recording was discontinued at 7:00 AM. The sleep records from the data collection nights were scored in 30-s bins using standard criteria by an experienced sleep technician and were reviewed by one of the investigators (E.O.B.). For each subject, the percentage of the 11:00 PM until 7:00 AM recording time spent awake or in stage 1, stage 2, SWS, or REM sleep was calculated. Both the technician and investigator (E.O.B.) were blinded to the treatment received by the subject.

As a subjective measure of sleep quality and quantity, subjects maintained a sleep diary for the duration of the study. For each night, they recorded estimates of the number of hours of sleep, number of awakenings, and sleep quality (0–10 scale).

Endocrine Measurements

At midnight, 3 AM, and 6 AM, 10-ml blood samples for measurement of cortisol and melatonin concentrations were drawn from the intravenous tubing outside the subject's room. After centrifugation, the plasma samples were stored at −70°C until they were analyzed as a batch. The plasma concentrations of cortisol and melatonin were measured in duplicate using a commercially available enzyme-linked immunosorbent assay kit (American Laboratory Products Company, Windham, NH). The average of the duplicate measurements was used as the value for each sample.

Subjects voided at 10:30 PM, and all urine produced until a 7:00 AM void was collected to measure excretion of urinary free cortisol and 6-sulfatoxymelatonin (6-SM), the chief metabolite of melatonin. The urine volume was measured, and samples were stored at −70°C until they were analyzed as a batch. The urinary concentrations of free cortisol and 6-SM were measured in duplicate using a commercially available enzyme-linked immunosorbent assay kit (American Laboratory Products Company). The products of the urinary volume and the measured concentrations of cortisol and 6-SM were used as the total nocturnal excretion.

Pulse Oximetry

Subjects wore a disposable finger pulse oximeter (N-200 Pulse Oximeter; Nelcor Inc., Hayward, CA), and the value was observed throughout the recording period for safety. The data, recorded every 5 s, were downloaded to a computer, and the average value for each minute was calculated. The mean value for the entire night and for each stage of sleep was determined. In addition, the number of minutes spent with a value below 95% and below 92% was calculated.

Statistical Analysis

The sample size of 10 was chosen to have 90% power to detect a 50% decrease in REM sleep time. For each stage of sleep or wakefulness, a repeated-measures analysis of variance (RM-ANOVA) model was constructed to detect a difference in the percentage of the recording time between the saline–placebo night and each of the three treatment conditions (SAS Statistical Software version 9.1; SAS Institute, Cary, NC). This approach was taken so that the different nights could be compared while taking into account the repeated measurements within each person. If the overall test comparing the four nights was significant at the 0.05 level, the pairwise comparisons of interest were performed.

For cortisol and melatonin, RM-ANOVA models were used to detect a difference in the serum concentration at any of the sampling times caused by melatonin or remifentanil. The sampling times were evaluated individually as well as combined by measuring the area under the curve of the nighttime measurements. The data for the individual sampling times as well as the area under the curve were log transformed to better approximate the normal distribution, which is the assumption of the statistical models. For the overnight total excretion of free cortisol and 6-SM, the data were again log transformed, and evaluated using a RM-ANOVA model to perform the paired t test comparing the two groups.

Results

Twelve healthy volunteers (table 1) enrolled in the study. Two withdrew after the first data collection night because of discomfort in the study environment and inability to adhere to the 4-week study schedule. On the remifentanil titration night, criteria for respiratory depression (respiratory rate $\geq$ 75% of baseline or oxygen saturation $\geq$ 97% of baseline) from remifentanil were present in three subjects at 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$, two subjects at 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and four subjects at 0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$. All subjects demonstrated some

Table 1. Demographics of Study Subjects

n enrolled/n completed	12/10
Age, median (range), yr	23.9 (20–35)
Sex, M/F	6/4
Height, median (range), cm	180 (163–193)
Weight, median (range), kg	75 (57–98)

Table 2. Respiratory Effect of Remifentanil

Subject No.	Oxygen Saturation, %		Breaths/min		Infusion, $\mu g \cdot kg^{-1} \cdot min^{-1}$
	Baseline	Remifentanil	Baseline	Remifentanil	
1	99	98	6	6	0.02
2	100	98	10	8	0.04
3	99	99	6	4	0.02
5	97	96	20	16	0.03
6	98	95	10	5	0.02
7	98	97	16	12	0.04
8	100	98	16	13	0.04
9	100	100	9	7	0.04
10	100	97	22	14	0.04
11	98	96	20	13	0.03

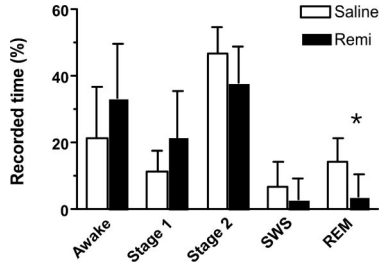

Fig. 2. Remifentanil effect on sleep. Polysomnography from the nights with a saline infusion *versus* the nights with a remifentanil infusion demonstrates a significant decrease in the percentage (mean ± SD) of time spent in REM sleep. * $P < 0.05$. REM = rapid eye movement sleep; Remi = remifentanil–placebo; Saline = saline–placebo; SWS = slow wave sleep.

degree of respiratory depression, but one subject did not meet the respiratory depression threshold even at 0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (table 2).

Polysomnography

The polysomnograms from one subject were unable to be retrieved from the computer. For the other nine subjects, technically adequate sleep recordings were obtained on 31 of the 36 nights of recording (table 3).

Compared with the saline–placebo night, there was a 72.3% decrease in REM sleep ($P < 0.05$) on the remifentanil–placebo night (fig. 2). On these nights, there was also a 52.9% decrease in SWS time and a 58% increase in wake time, but these changes were not statistically significant.

Melatonin did not cause a statistically significant change in the percentage of the recording period spent in any stage of sleep or wakefulness. Of specific interest, administration of melatonin did not restore the amount of SWS or REM sleep on the remifentanil infusion nights. Although not statistically different, there was actually less REM sleep on the remifentanil–melatonin night than on the remifentanil–placebo night.

The results of the subjective sleep measures were consistent with the polysomnographic results (fig. 3). The estimated number of awakenings was greatest ($P = 0.058$) on the remifentanil–placebo night (remifentanil–placebo *vs.* saline–placebo, $P = 0.040$; remifentanil–placebo *vs.* saline–melatonin, $P = 0.010$). Similarly, the estimated number of hours of sleep was lowest on the remifentanil nights with some increase in estimated sleep in the melatonin group (RM-ANOVA $P = 0.006$, pairwise comparisons: remifentanil–placebo *vs.* saline–placebo, $P = 0.004$; remifentanil–placebo *vs.* saline–melatonin, $P = 0.001$; remifentanil–placebo *vs.* remifentanil–melatonin, $P = 0.039$). Remifentanil reduced sleep quality. This reduction was not significantly improved by melatonin (RM-ANOVA $P = 0.029$, pairwise comparisons; remifentanil–placebo *vs.* saline–placebo, $P = 0.023$; remifentanil–placebo *vs.* saline–melatonin, $P = 0.008$). Subjects reported feeling more tired after the remifentanil infusion ($P < 0.001$).

Circadian Hormones

The remifentanil infusion did not alter the plasma levels of melatonin at any of the sampling times during the night. Both the saline–placebo group and the remifentanil–placebo groups demonstrated a normal 3:00 AM peak (fig. 4A), with no statistically significant differences in the area under the curve of the midnight, 3:00 AM, and 6:00 AM plasma concentrations. Consistent with these findings, the total nocturnal urinary excretion of 6-SM, melatonin's chief metabolite, was 0.0126 ± 0.0080 mg in the saline–placebo group and 0.0141 ± 0.0125 mg in the remifentanil–placebo group ($P = 0.91$). On the nights when melatonin was administered, melatonin and 6-SM were assayed only to confirm the presence of supranormal concentrations, but dilutions to determine the precise concentration were not performed.

Remifentanil suppressed the morning increase in the plasma concentration of cortisol (fig. 4B). This finding was corroborated by significantly lower nocturnal uri-

Table 3. Percentage of Night Spent in Each Sleep Stage

Treatment	Awake	Stage 1	Stage 2	SWS	REM
Saline–placebo	21.2 ± 15.4	11.4 ± 6.1	46.7 ± 7.8	6.8 ± 7.6	14.1 ± 7.2
Remifentanil–placebo	33.5 ± 16.3	21.6 ± 14.2	37.9 ± 11.1	3.2 ± 6.1	3.9 ± 6.9*
Saline–melatonin	28.6 ± 14.9	11.8 ± 6.5	45.6 ± 9.7	5.5 ± 6.9	8.5 ± 7.8
Remifentanil–melatonin	33.2 ± 19.4	14.1 ± 10.3	46.0 ± 18.6	3.7 ± 5.6	2.8 ± 5.8

Values are mean ± SD.

* Significantly less than on saline infusion night ($P \leq 0.05$).

REM = rapid eye movement sleep; SWS = slow wave sleep.

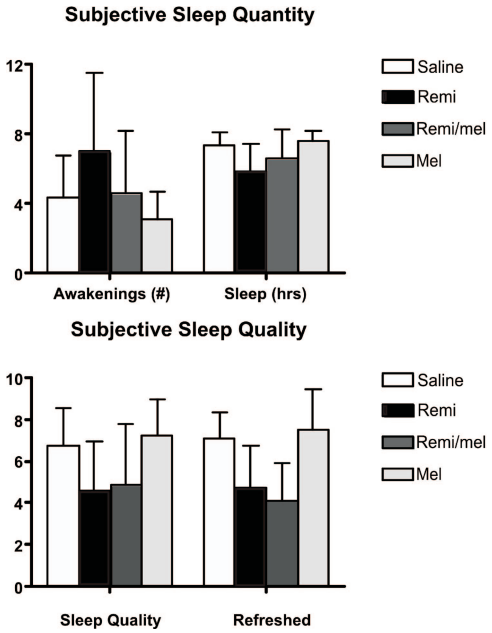

Fig. 3. Subjective sleep measures. The results (mean ± SD) from subjects' sleep diary entries regarding sleep quantity and quality on the morning after the study night are presented. There is a trend ($P = 0.058$) toward increased number of awakenings in the remifentanil–placebo (Remi) group, and there is a significantly lower estimate of sleep time in the remifentanil–placebo group ($P = 0.006$) with some evidence ($P = 0.039$) of increased subjective sleep time in the remifentanil–melatonin (Remi/mel) group. Both measures of sleep quality were significantly reduced in the remifentanil infusion groups ($P = 0.029$ for sleep quality and $P = 0.001$ for awoke feeling tired *vs.* refreshed). Melatonin did not ameliorate remifentanil's effect on sleep quality. Mel = saline–melatonin; Saline = saline–placebo.

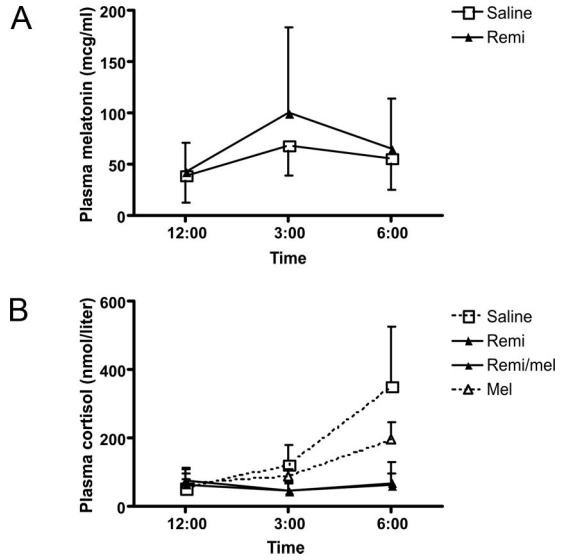

Fig. 4. Melatonin and cortisol plasma concentrations. The plasma melatonin (*A*) and cortisol (*B*) concentrations (mean ± SD) measured at midnight, 3:00 AM, and 6:00 AM are presented. *A* demonstrates the normal nocturnal increase and decrease of melatonin in both the saline–placebo (Saline) and remifentanil–placebo (Remi) groups. In the saline–melatonin (Mel) and remifentanil–melatonin (Remi/mel) groups, the plasma concentrations of melatonin were measured only to confirm the presence of supranormal concentrations. *B* demonstrates the suppression of plasma cortisol concentrations by remifentanil, which became statistically significant at the 6:00 AM time point. Melatonin did not have a statistically significant effect on the cortisol concentration at any single time point, but the area under the curve demonstrated suppression of cortisol concentrations by melatonin ($P = 0.045$).

nary free cortisol excretion in the remifentanil–placebo group than in the saline–placebo group (fig. 5).

Discussion

The principal finding of this study is that a constant infusion of the opioid remifentanil reduces the amount of nocturnal REM sleep without disturbing the circadian pacemaker. Melatonin administration neither altered normal nocturnal sleep nor prevented remifentanil-induced sleep disturbance. This study confirms previous findings of opioid sleep disturbance in humans[7–12] and extends them by demonstrating that the opioid effects occur even at low constant doses, and that the mechanism for this sleep disturbance is not opioid disturbance of the circadian pacemaker.

The paradoxical inhibition of human sleep by a narcotic, first reported in 1969, was demonstrated in eight incarcerated former narcotic addicts.[7] An intramuscular injection of 7.5, 15, and 30 mg/70 kg body weight of morphine at 10:00 PM dose-dependently decreased nocturnal SWS and REM sleep and increased stage 1 and stage 2 non-REM sleep and wakefulness. These findings have been expanded by a recent study in seven opioid-naive healthy volunteers.[12] All of these studies administered the opioid before the sleep recording period, and the observations reflect the response to either the presence of opioid or the decrease of opioid concentration. In the current study, the infusion of remifentanil permitted maintenance of a constant opioid concentration throughout the sleep recording period.

The sleep inhibition caused by a constant opioid concentration is similar to that reported previously under conditions of decreasing opioid concentrations. Although remifentanil did inhibit REM sleep, the normal distribution of REM sleep, occurring predominantly later in the night, was preserved (table 4). This uniformity of effect throughout the night suggests that opioid inhibi-

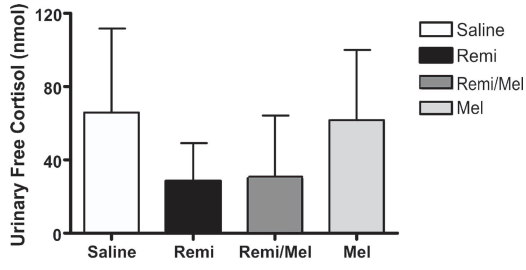

Fig. 5. Urinary free cortisol. The total excretion of urinary free cortisol (mean ± SD) from 10:30 PM until 7:00 AM reveals a significant decrease in cortisol excretion in the remifentanil–placebo (Remi) group. * $P = 0.004$. Mel = saline–melatonin; Remi/mel = remifentanil–melatonin; Saline = saline–placebo.

Table 4. Percentage of Time in Slow Wave and Rapid Eye Movement Sleep by Thirds of the Night

	Saline–Placebo	Remifentanil–Placebo	Remifentanil–Melatonin	Saline–Melatonin
Slow wave sleep				
First third	20.0 ± 21.6	8.5 ± 20.0	8.0 ± 15.8	16.8 ± 24.2
Middle third	12.1 ± 14.7	6.9 ± 13.5	7.8 ± 11.8	6.4 ± 15.7
Last third	0.0 ± 0.0	0.0 ± 0.0	1.3 ± 3.7	3.5 ± 6.5
Rapid eye movement sleep				
First third	6.0 ± 6.3	4.5 ± 12.7	1.6 ± 4.4	5.6 ± 6.5
Middle third	22.5 ± 10.7	2.6 ± 4.9	3.7 ± 6.2	17.6 ± 17.7
Last third	39.1 ± 22.5	10.9 ± 17.4	8.4 ± 19.4	19.2 ± 19.6

Values are mean ± SD.

tion of sleep does not work through the arousal mechanisms of opioid withdrawal.

In this study, the lowest dose of remifentanil that evoked a definite but slight physiologic effect was specifically chosen to minimize opioid side effects such as nausea or pruritus that might inhibit sleep. The 53% reduction in SWS and the 72% reduction in REM sleep time resulting from the low-dose remifentanil infusion are relatively modest compared with the abolition of both SWS and REM sleep by a 30-mg/70-kg dose of morphine. These less extreme changes are consistent with the dose-dependent nature of opioid sleep inhibition,[7] and might also reflect the unusually high percentage of time awake and in stage 1 non-REM sleep and the unusually low percentage of time spent in SWS and REM sleep[30] on the control (saline/placebo) night. Even with the low dose of remifentanil and the unusually poor sleep on the control night, our subjects had both subjective increases in wakefulness and objective decreases in sleep caused by remifentanil.

The low dose of remifentanil did provide a slight degree of respiratory depression on the remifentanil infusion nights (table 5). Melatonin, alone or in combination with remifentanil, did not cause any respiratory suppression. In this study, the arterial concentration of carbon dioxide was not measured; however, the role of hypercarbia in opioid inhibition of sleep bears investigation because a 15-mmHg increase in arterial carbon dioxide concentration usually causes awakening.[31]

Contrary to the hypothesis of this study, the opioid-induced sleep disturbance was not associated with suppression of the nocturnal melatonin surge, suggesting that this sleep disturbance is not secondary to a circadian pacemaker disturbance. The 3:00 AM plasma melatonin concentration and the overnight urinary 6-SM excretion were not suppressed by remifentanil, nor was exogenous administration of melatonin able to ameliorate the remifentanil-induced sleep disturbances. Remifentanil did prevent the normal circadian increase in 6:00 AM cortisol concentration. This finding, however, is consistent with the established ability of opioids to block the production of cortisol.[32]

Efforts to understand the mechanisms causing opioid-induced REM sleep inhibition have focused on cholinergic neurotransmission. Opioid receptors and their stimulation of G-protein activity in REM sleep–related nuclei by opioid exposure has been demonstrated in a rat brain slice preparation.[33] In the anesthetized cat, microdialysis administration of morphine into the medial pontine reticular formation, a key area in REM sleep generation and homologous to one of the G protein opioid-activated areas in the rat, inhibits acetylcholine release.[34] A series of behavioral experiments in chronically instrumented and unmedicated cats has demonstrated that microinjection of opioid into the medial pontine reticular formation causes dose-dependent, naloxone-reversible,[35] and μ receptor–selective[36] inhibition of REM sleep. Opioids,[37] along with most state-altering drugs administered by anesthesiologists,[38] act directly on the neural network controlling sleep and arousal.

The absence of remifentanil suppression of nocturnal melatonin secretion in our volunteers means that the best available evidence favors activation of opioid receptors on specific sleep-related nuclei as the mechanism for opioid-induced sleep disturbance. Currently, therapeutic options for increasing REM sleep and SWS are limited. A practical means of minimizing opioid-induced sleep inhibition is to maximize use of nonopioid analgesic techniques.

Although this study demonstrates that even a low dose of opioid has a profound inhibitory effect on nocturnal

Table 5. Overnight Pulse Oximetry Values

	Saline–Placebo	Remifentanil–Placebo	Remifentanil–Melatonin	Saline–Melatonin
Average, %	97.74 ± 0.76	97.41 ± 1.05	97.10 ± 1.37	97.87 ± 0.70
Number of minutes with value <95%	1.86 ± 2.86	10.23 ± 21.67	24.85 ± 48.02	0.73 ± 0.61
Number of minutes with value <92%	0.05 ± 0.11	0.62 ± 1.37	0.47 ± 0.88	0.08 ± 0.11

Values are mean ± SD.

REM sleep in healthy volunteers, the clinical significance of opioid-induced sleep disturbance using higher doses of opioid in patients with painful conditions is undefined. Sleep disturbance is common in patients taking opioids, but these patients also have painful conditions that can inhibit sleep. Possible consequences of opioid-induced sleep inhibition—including dysphoria, delirium, and immunosuppression—are important concerns in postoperative patients, but the contribution of sleep inhibition toward causing these morbidities is unquantified. Further studies in these complicated patients are required to establish the clinical significance of both the opioid effect on sleep in patients and the role of sleep deprivation in morbidity.

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