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The Effect of Opioids on Sleep Architecture

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Study Objectives: The effect of opioid medications on sleep architecture has been demonstrated in patients with comorbid pain or opioid addiction. This study examined whether commonly used opioid medications have an adverse effect on sleep architecture in healthy adults.

Methods: Forty-two healthy subjects were examined with polysomnography after a bedtime dose of placebo, sustained-release morphine sulfate (15 mg), or methadone (5 mg) on each of 3 different nights in a double-blind multiple crossover study in a sleep laboratory in the General Clinical Research Center at an academic medical center.

Results: Both opioid drugs significantly reduced deep sleep and increased stage 2 sleep (both $p < .01$); neither had an effect on sleep efficiency, wake after sleep onset, or total sleep time.

Conclusions: Single doses of oral opioid medications can significantly affect sleep architecture in healthy adults, and observed reductions in slow-wave sleep following opioid administration may have important implications for the pathogenesis of opioid-use related fatigue.

Keywords: Sleep, polysomnography, opioids, pain, pharmacology

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A small number of older studies, performed mainly on current or former addicts, report that opioids, while sedating, actually interrupt sleep.[1-5] These studies demonstrate that opioids increase wakefulness and the number of shifts in sleep-waking states[2] and decrease total sleep time,[2] sleep efficiency,[2,4] delta sleep,[2,4] and rapid eye movement (REM) sleep.[2,3] Other studies, examining postoperative patients, have also shown a reduction of slow-wave sleep with opioid administration.[6]

If these effects generalize to other groups of patients, the potential sleep disruption from opioid use may contribute to the sedation and fatigue that are commonly noted in patients receiving opioid therapy.[7] However, when evaluating prior studies on the effects of opioids on sleep architecture, it is difficult to differentiate the effects of the opioid medication from the effects of the underlying disorders (eg, addiction/dependence, postoperative pain). A recent paper, from an anesthesia perspective, examined sleep architecture in 7 healthy subjects in response to acute intravenously administered morphine.[8] The investigators found that morphine led to reductions in slow-wave sleep and somewhat smaller reductions in REM density but did not increase awakenings or arousals.

This study replicates and extends these observations on opioids and sleep. In a group of 42 healthy patients, we wondered if commonly prescribed oral opioids would have an adverse effect on sleep, similar to the effect observed in Shaw et al's study of 7 patients' response to intravenously administered morphine. Furthermore, because animal studies have suggested that opioid effects on REM sleep are mediated by μ receptors,[9] we wondered if different classes of opioids might act differently. We hypothesized that morphine, a relatively pure μ agonist,[10] would have particular effects on REM sleep[9], whereas methadone, a μ agonist with NMDA antagonist properties,[11,12] would have increased actions on non-REM (NREM) sleep.[13]

METHODS

Eligible subjects (see below) were studied in this double-blind cross-over protocol on 3 admissions to the General Clinical Research Center Gillin Laboratory of Sleep and Chronobiology at University of California, San Diego. Each admission lasted 2 nights. The first night was an acclimation night; patients received the study drug at 8:00 pm on the second night. Data from the sleep recordings from the second night of each admission are the focus of this study. Subjective fatigue measures were collected using the Multidimensional Fatigue Symptom Inventory Short Form (MFSIsf) and the Profile of Mood States (POMS) at baseline and in the morning following each drug administration. To control for potential order effects, the sequence of drug administration was randomized for each subject. All drug administration was according to a double-blind protocol. On 1 admission, patients received oral placebo. The other admissions provided 5 mg methadone or 15 mg sustained-release morphine sulfate by mouth. Each admission was separated by at least 1 week. The UCSD Institutional Review Board approved the study.

Subjects

Eligible subjects were between 18 and 60 years of age and were not taking any medication on an ongoing basis. All subjects were healthy and had no history of substance abuse. Power

Disclosure Statement

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Table 1—Sleep Architecture in Response to Opioids

	Placebo	Morphine	Methadone	$F_{2,82}$, p
TST, min	391.393 ± 6.415	383.286 ± 8.936	386.476 ± 6.584	0.748, .442
Sleep efficiency	89.136 ± 0.999	87.133 ± 1.736	89.362 ± 1.030	1.553, .222
Wake after sleep onset	28.726 ± 3.493	39.814 ± 6.665	28.095 ± 2.742	2.844, .080
Arousal Index	5.986 ± 0.570	5.214 ± 0.497	4.419 ± 0.381	5.201, .008
Sleep stage, as a % of TST				
REM	22.219 ± 0.813	22.410 ± 0.765	20.688 ± 0.919	2.370, .110
1	7.702 ± 0.605	8.698 ± 0.667	7.921 ± 0.452	1.802, .172
2	58.491 ± 1.422	61.310 ± 1.130	63.767 ± 1.290	12.160, .001
3	6.583 ± 0.556	4.931 ± 0.551	5.117 ± 0.634	7.063, .002
4	5.095 ± 0.823	2.657 ± 0.533	2.021 ± 0.461	16.607, .001
AHI	3.160 ± 0.613	2.748 ± 0.424	2.081 ± 0.371	7.996, .007

Polysomnographic measures of sleep architecture after single-dose administration of each medication. Data are presented as mean ± SEM. n = 42 for all analyses. (Arousal index based on: arousal = increase in electroencephalographic frequency ≥ 3 seconds duration, following ≥ 10 seconds of sleep.) TST refers to total sleep time; AHI, apnea-hypopnea index.

analyses suggested that a sample size of 50 would result in 80% power to detect a significant ($p < .05$) difference in main outcome measures.

Sleep Monitoring

All sleep variables were obtained using the 16-channel GRASS Heritage polysomnographic recording system (model PSG36-2, West Warwick, RI), which measured the following bioelectric signals: central and occipital electroencephalogram, bilateral electrooculogram, submental electromyogram, thoracic and abdominal respiratory effort, airflow (via both thermistor and nasal cannula pressure-transducer), electrocardiogram, tibialis electromyogram, and oximetry. Sleep records were scored by an experienced polysomnographic technologist according to the standard criteria of Rechtschaffen and Kales.[14] Records were scored for total sleep time, number of minutes of wake after sleep onset, number of awakenings, sleep latency, sleep efficiency, and percentage of stages 1, 2, 3, 4, and REM sleep, as well as for cortical arousals (defined as sudden increases in electroencephalogram frequency of at least 3 seconds duration, following at least 10 seconds of continuous sleep, with or without accompanying muscle activity). Because variability exists in the literature regarding the importance—and the appropriate level—of oxyhemoglobin desaturation for respiratory events, oxyhemoglobin desaturation was not part of our criteria for scoring respiratory events. Hypopneas were defined as a drop in pressure-transducer airflow to 10% to 50% of baseline; apneas were defined as a drop in pressure-transducer airflow to less than 10% of baseline. The apnea-hypopnea index and arousal index were calculated by total number of apneas + hypopneas or total number of arousals divided by total sleep time.

Statistical Analysis

Data were examined with SPSS software (version 11.0, SPSS Inc., Chicago, IL). After confirming that there was no effect of order of administration on the measurements, data from each medication were consolidated, and repeated measures analyses of variance (ANOVA) were performed contrasting sleep architecture, apnea-hypopnea index, arousal index, and the MFSIsf and POMS under each of the 3 drug conditions, using a 2-tailed table. When ANOVA revealed the existence of significant ($p < .05$) within-subjects effects of drug treatment, posthoc analysis was done to allow pairwise comparison of main effects using Bonferroni adjustment. Unless otherwise stated, data are presented as mean ± standard error of the mean (SEM).

RESULTS

Of the 46 participants that entered the study, 42 completed all 3 hospitalizations. The other 4 dropped out for diverse reasons (scheduling conflicts, moving away from San Diego); analyses are based on data from subjects who completed all hospitalizations. The average age of subjects was 27.0 ± 1.2 years; 40.5% of the subjects were men. The subjects' ethnic makeup was as follows: 57% Caucasian, 7% Black, 12% Hispanic, 19% Asian, and 5% other. The subjects' mean body mass index was 24.29 ± 0.62 kg/m^2.

One subject became lightheaded 1 hour after medication administration, and 2 subjects reported nausea upon waking; these symptoms subsided quickly, and all subjects were able to complete the study without intervention.

Table 1 summarizes the effects of the drugs on sleep architecture. Both opioids increased the percentage of time spent in light sleep ($p < .001$) (stage 2) and substantially decreased the percentage of time in deep sleep (stages 3 and 4) ($p < .001$, see figure 1). No drug effects were seen on sleep efficiency, total sleep time, wake after sleep onset, or subjective measures of mood or fatigue (POMS and MFSIsf). Compared with placebo, methadone administration was associated with small but significant reductions in both the arousal index ($p < .01$) and apnea-hypopnea index ($p < .01$), effects not observed with sustained-release morphine sulfate administration.

DISCUSSION

We observed that orally administered opioid drugs, even in low doses, decrease deep sleep, with an accompanying increase in percentage of stage 2 sleep. The change in percentage of deep sleep is impressive, as it represents a 30% to 50% decrease in stage 3 and stage 4 sleep.

As mentioned above, there are very few studies in this area. The majority of previous studies that reported an adverse effect of opioids on sleep appear to have relied on different subject populations, including current and former drug addicts.[1-5] In a review of this older literature, Moore and Dimsdale[15] commented

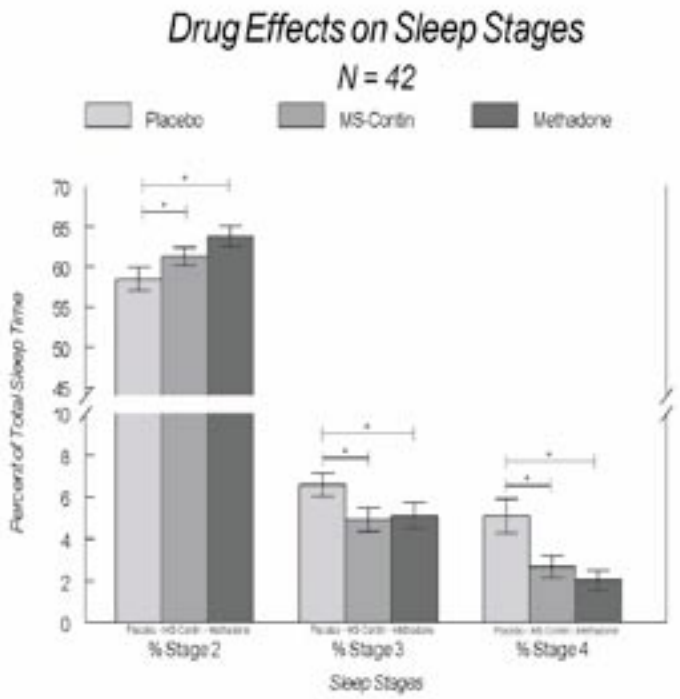

Figure 1—Percentage of total sleep time spent in stage 2, 3, and 4 sleep following administration of each medication. *Denotes significant ($p < .05$) difference in percentage compared to placebo.

that morphine and its congeners appeared to suppress REM sleep and increase nocturnal wake time (in terms of prolonged sleep latency and increased awakenings across the night). In addition, the drugs disturbed NREM, particularly slow-wave sleep.

As did Shaw et al,[8] we found that single doses of opioids in otherwise-healthy adults reduced slow-wave sleep but did not affect sleep efficiency or total sleep time. However, unlike Shaw et al, we did not find a significant reduction in REM sleep with single-dose oral administration of morphine or methadone. Opioid effects on REM sleep may be dose dependent, as high-dose tramadol, an opioid with μ agonist and norepinephrine and serotonin reuptake-inhibitor properties, has been demonstrated to reduce duration of REM sleep, a finding not observed with low-dose tramadol.[16] It is possible that REM sleep inhibition would have also appeared in our study, had higher doses of morphine or methadone been used.

We did not observe a change in the apnea-hypopnea index or arousal index following morphine administration; however, small reductions in both of these indexes were seen following methadone administration. Although statistically significant, the magnitude of reductions in the arousal and apnea-hypopnea indexes (1.6 and 1.1 events/hour, respectively) was small, and unlikely to be clinically significant. In prior studies, long-term opioid use has been associated with an increase, rather than decrease, in respiratory events (notably central sleep apnea).[17,18] A change in sleep-disordered breathing event frequency has not been observed, however, in prior studies of short-term opioid administration.[19]

Our study has a number of limitations. First off, we cannot say whether this impact on sleep persists with chronic dosing of opioids. It is interesting to note that tolerance develops at different rates; ie, tolerance to opioid side effects such as constipation develops more rapidly than tolerance to their analgesic properties.[20] It is unknown whether or how rapidly one develops tolerance to the sleep effects of opioids. Although 1-time dosing of opioid medications did not result in significant changes in the subjective measures of fatigue, alteration in sleep architecture, if persistent with long-term opioid use, may contribute to the fatigue commonly experienced with opioid medications. This might be addressed more readily with animal experiments, as it would be difficult to model chronic opioid use in humans because of risks of dependency and withdrawal.

A second potential limitation is that our sample primarily reflects young adults (ages 18-35); only 3 of our subjects were older individuals. Given that sleep differs throughout the lifespan, one cannot be sure if our findings would generalize to an older population.

A third limitation is that we studied only principal measures of sleep architecture, arousals, and respiratory events. As the significance of additional sleep electroencephalographic features becomes more recognized, future studies may expand to include analyses of opioid effects on delta-wave amplitude and frequency, and cyclic alternating pattern versus non-cyclic alternating pattern sleep.

Lastly, this study was limited to pain-free normal subjects. If these study findings extend to patients experiencing pain, the sleep effects of opioids may have important clinical consequences. Pain itself has a prominent effect on sleep,[21-24] and the sleep-altering properties of these drugs may further contribute to the fatigue reported by patients on chronic therapy. In addition, because animal and human studies have demonstrated that experimentally induced sleep disruption lowers the threshold for detection of painful stimuli,[25-28] the sleep effects of opioids may have interesting implications on pain itself. Although opioids are obviously helpful for pain, one could speculate that, by virtue of their sleep-altering properties, opioids could paradoxically result in a reduction in the threshold for pain stimuli. This could result in a vicious circle, requiring that continuing or even higher doses of opioids are required for pain relief. This matter would have to be addressed by differently designed studies. Such studies might examine opioid effects on sleep in normals subjected to experimental pain stimuli or in medical patients reliably experiencing pain so that their opioid use may be anticipated (eg, molar teeth extraction). If such observations hold up with replication, then they suggest new strategies for pain treatment in the setting of opioid usage. In such a setting, use of a sedative-hypnotic with broad actions on sleep, or perhaps one that focused particularly on deep sleep, may help raise the pain threshold, thereby leading to further reductions in opioid use.

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