Acute Intravenous Administration of Morphine Perturbs Sleep Architecture in Healthy Pain-Free Young Adults: a Preliminary Study

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Study Objectives: Pain is a leading cause of sleep disturbances in medical illness. Providing effective analgesia is considered an important intervention to reduce these sleep disturbances. Opioids remain the treatment of choice to relieve postoperative pain in hospitalized patients. However, their effects on sleep in pain patients or normal subjects remain unclear, as previous studies have been conducted mainly with former opioid addicts. The purpose of this investigation was to evaluate and describe the effects of acute clinical doses of morphine on sleep in healthy pain-free subjects.

Design: Subjects were randomly assigned to untreated (baseline), morphine (intravenous injections of 0.1 mg/kg), and placebo (intravenous injections of 0.9% NaCl) conditions.

Setting: Sleep laboratory.

Participants: Seven healthy pain-free, nonaddicts (5 women, 2 men; mean age = 25 ± 1.6 years).

Measurements and Results: Standard polysomnographic sleep and respiratory variables were measured during 3 experimental conditions. The treatment effect was analyzed with a Latin square cross-over design followed, when appropriate, by Tukey contrasts. Morphine altered sleep architecture by reducing slow-wave sleep (non-rapid eye movement stages 3-4) and rapid eye movement sleep, and by increasing non-rapid eye movement stage 2 sleep. Results did not reveal any statistical differences for other sleep and respiratory variables.

Conclusions: Similar to earlier findings in animals, nondependent opioid addicts, and postoperative patients, morphine was found to reduce duration of slow-wave sleep. Unlike previous reports, however, its acute administration produced a moderate reduction in rapid eye movement sleep and did not increase correlates of arousal (ie, awakenings, electroencephalogram arousals, wake after sleep onset). Future studies should correlate these findings in patients with pain and evaluate whether optimal pain relief with opioid therapy can improve sleep disturbances in pain patients.

Key words: REM, sleep, morphine, SWS sleep, healthy subjects.

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INTRODUCTION

ONE OF THE LEADING CAUSES OF SLEEP DISTURBANCES IN MEDICAL ILLNESS IS PAIN. SLEEP DISTURBANCES ARE REPORTED BY MORE THAN 70% OF patients suffering from painful disorders, including chronic rheumatic diseases, headaches, postherpetic neuralgia, burn injuries, and postoperative pain to name a few.1-5 Pain and other elements of the illness influence and alter the sleep process.6 Reciprocally, disturbances in sleep structure may decrease pain thresholds and interact with the illness and further contribute to daytime symptoms.3,5,6

Even though there are limited data suggesting that pain relief is sufficient to improve sleep in patients with acute or chronic pain, it is often assumed that effective pain relief is the most helpful intervention to reduce sleep disturbances in such patients.4,7 However, most medications used to treat pain also alter sleep architecture. For example, studies have shown that analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs can increase awakenings and reduce both slow-wave sleep (SWS) and rapid-eye movement (REM) sleep.8,9 Although animal studies show that opioids alter sleep,10-12 there is a paucity of information on the effects of opioids on sleep in humans in pain. For example, 1 study observed sleep disturbances in hospitalized patients after the administration of morphine or other opioids.13 Nonetheless, studies conducted in clinical settings are also faced with many other confounding factors such as pain, anxiety, and nonconducive sleep environment and are, therefore, not able to establish independent effects of morphine on sleep. Furthermore, a recent study suggests that severe sleep disturbances are present in a postoperative setting regardless of whether patients received local anesthetics or opioids.14

There are surprisingly few experimental studies describing the effects of morphine or other opioids on normal human sleep. In fact, other than the little information from published abstracts,15,16 the current state of knowledge on this subject originates mainly from the evaluation of former opioid-dependent prisoners.17-19 Even though these studies did not use standard sleep-scoring criteria, their results suggest that morphine increases nocturnal wakefulness and decreases REM and SWS sleep in a dose-dependent manner.17-19 However, this may not be the case clinically, as most patient populations comprise of individuals with little or no prior exposure to opioids. Furthermore, when former opioid addicts are compared with normal subjects, they show a differential

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arousal response to morphine, which could be expected to be carried through the sleep state. Therefore, the purpose of the present study was to evaluate the effects of clinically relevant doses of morphine on sleep in healthy pain-free young adults with no prior history of opioid addiction or abuse. Based on the few available studies, we expected to find a decrease in total sleep time (TST), characterized by diminished SWS and REM sleep. Further, we hypothesized that the arousal response (ie, awakenings, electroencephalogram [EEG] arousals) to morphine during sleep would be minimal in our sample of normal subjects.

MATERIALS AND METHODS

Participants

Seven healthy subjects (5 women, 2 men) between 24 and 28 years of age (mean age = 25 ± 1.6 years) and weighing an average of 70 kg (SD = 15.1) participated in the study. All of them met the selection criteria listed in Table 1 and provided written informed consent. Prior to the study, subjects were habituated to the sleep-laboratory environment of the Centre hospitalier de l’Université de Montréal and were screened for possible sleep disorders (ie, apnea, insomnia, periodic limb movements) via polysomnography. During the habituation night, subjects slept with intravenous apparatus taped in place, but no injections were performed. Participants’ general health condition was evaluated by 1 of the investigators (PM). All subjects showed normal sleep patterns; were judged to be healthy; and, confirmed by self report, not to be using any medical or recreational drugs, although this was not verified by blood or urine analysis.

Procedures

The study protocol was approved by the Scientific and Ethics Committees of the Centre hospitalier de l’Université de Montréal, and all the procedures and risks were carefully explained to the subjects, who were paid for their participation. After the habituation night, the study consisted of 3 nights in the sleep laboratory. Subjects were randomly assigned to untreated (baseline), morphine, and placebo conditions (Table 2) conducted in a single-blind manner, as requested by the Ethics Committee. Because of possible sleep alterations induced by procedures and treatment conditions, experimentation nights were performed at weekly intervals over a 3-week period to avoid confounding effects. On each occasion, subjects received either intravenously administered (IV) injections of morphine or placebo solution (0.9% NaCl) or slept under baseline conditions. Subjects were instructed to keep the same regular home sleep-wake schedule during the study and not to take any medication during the day of the experimentation. Subjects were contacted prior to their arrival at the laboratory to confirm that they were not experiencing any pain (eg, headache, cramps) or taking any medication. During the evening, participants answered questionnaires on the quality of sleep during the preceding week using an adapted weekly version of the Pittsburgh Sleep Quality Index. Participants’ safety during the experimental nights was ensured by close monitoring of respiratory parameters and by the presence of a physician in the sleep laboratory during the whole night. In the morning, participants were asked to rate sleep quality on a 10-cm visual analogue scale (0 = slept very poorly; 10 = slept very well) and to complete other sleep measures. Dream content was also recorded (data not reported here).

Slow IV injections of morphine sulfate (0.1 mg/kg) or placebo (equal volume of 0.9% NaCl) were administered via a catheter fixed on the subject’s arm and connected to an infusion pump (Baxter Healthcare Corporation, Deerfield, Ill) located outside the room where subjects slept. A first bolus injection was given 30 to 60 minutes before the lights were turned off, and a second one was administered when subjects were asleep at the midpoint of the night between 3:00 and 4:00 AM. To keep the IV line patent, subjects were given 0.9% NaCl at a rate of 10 mL per hour. To ensure proper drug delivery, each injection was followed by a bolus (10 mL) of normal saline. Furthermore, the IV line was

| Table 2—Study Design: Order of Experimental Conditions |
|-------------|-------------|
| Subject | Night | Experimental Conditions |
| 1 | 1 | Placebo |
| 2 | 1 | Baseline |
| 3 | 1 | Morphine |
| 2 | 1 | Baseline |
| 3 | 1 | Morphine |
| 3 | 1 | Placebo |
| 4 | 1 | Placebo |
| 5 | 1 | Baseline |
| 2 | 1 | Morphine |
| 3 | 1 | Placebo |
| 6 | 1 | Morphine |
| 2 | 1 | Placebo |
| 3 | 1 | Baseline |
| 7 | 1 | Morphine |
| 2 | 1 | Placebo |
| 3 | 1 | Baseline |

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verified 30 minutes before the second injection (morphine or placebo) by entering the room. This procedure was repeated during the baseline night between 2:00 and 3:00 AM, during which time 0.9% NaCl was also infused at 10 mL per hour while the subjects were asleep.

To avoid respiratory depression and to ensure participants’ safety, respiratory parameters were closely monitored using a standardized intervention protocol irrespective of the treatment condition: in the event of a respiratory rate below 8 per minute or oxygen saturation below 93%, 4 L per minute of oxygen was to be administered to the subject via facemask together with IV boluses of 0.01 mg of naloxone per minute (1 mL [0.4 mg] of naloxone diluted in 9 mL of 0.9% NaCl) until a respiratory rate of 12 per minute was reached. Because morphine can also induce nausea and vomiting, dimenhydrinate (50 mg IV in 100 mL D5% over 30 minutes) was given in the laboratory as needed and supplemented with 2 oral doses (50 mg) during the day.

Polysomnographic recordings were performed digitally using a portable system (Suzanne model V-70608-00, 2001 Nellcor Puritan Bennett, Ottawa) for all subjects. Standard sleep variables were monitored: EEG derivations from C4A1 and O1A2 (120 Hz monopolar); electrooculogram for eye movements, electromyogram for chin and right and left anterior tibialis, and electrocardiogram for heart rate (bipolar). Other sensors included respiratory-effort belts (thorax, abdominal), nasal and oral airflow, and an oximeter. Participants were also monitored with a video camera and a microphone to record snoring.

Data and Statistical Analyses

Sleep was visually scored according to a standard method22 with Sandman software (version 6.1, Nellcor Puritan Bennett, Melville Ltd., Ottawa) by trained technicians blinded to experimental conditions. EEG arousals (ie, including those following movement, breathing events, or spontaneous) were scored according to American Sleep Disorder Association criteria.23 Alpha-delta characteristic, related to disturbed sleep, was described as low-frequency (0.5- to 3.5-Hz), high-amplitude waves (delta = 75 mV high) with superimposed high-frequency, low-amplitude alpha activity (8-12 Hz). Other sleep variables included TST (total minutes scored as sleep), sleep latency (number of minutes from lights out until the first epoch scored as sleep), sleep efficiency (total sleep time as a percentage of time in bed), number of awakenings during sleep, number of sleep-stage shifts during the night, and time spent in each sleep stage: non-rapid eye movement (NREM) stage 1, NREM stage 2, SWS (stages 3 and 4), and REM sleep (all expressed as a percentage of TST). Rapid-eye-movement density (ie, index of eye movement per total REM minutes) was also included. Subjective sleep variables were measured by asking the participants to estimate TST, sleep latency, number of awakenings, and sleep quality. The treatment effect

<table>
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<th>Table 3—Comparative Results Between the Treatment Conditions on Sleep and Respiratory Variables</th>
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<tr>
<td>Variables</td>
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<tr>
<td>TST, min</td>
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<tr>
<td>NREM Stage 1, %</td>
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<td>NREM Stage 2, %</td>
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<td>SWS, %</td>
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<td>REM, %</td>
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<td>REM periods, no.</td>
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<td>REM density, index</td>
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<td>SL, min</td>
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<td>WASO, min</td>
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<td>AW, no.</td>
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<td>AI</td>
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<td>SSS</td>
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<td>AHI</td>
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<td>UAR, index</td>
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<td>Snore, min</td>
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Data are presented as means (SEM). P values for main effects are presented or otherwise mentioned. TST refers to total sleep time; NREM, non-rapid-eye movement; SWS, slow-wave sleep; REM, rapid eye movement; SE, sleep efficiency; SL, sleep latency; WASO, wake time after sleep onset; AW, awakenings; AI, arousal index: number of arousals per hour of sleep; SSS, sleep-stage shifts: number of shifts for the TST; AHI, apnea-hypopnea index: number of apneas and hypopneas per hour of sleep; UAR, upper airway resistance; P, placebo; B, baseline; M, morphine.
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was analyzed with a Latin square cross-over design followed, when appropriate, by Tukey contrasts. The analyses were done with mixed procedure of SAS statistical software (version 8, SAS Institute, Inc., Cary, NC). Corrected $P$ values are reported, and $P < .05$ values were considered to be statistically significant.

RESULTS

Subjects’ results on the Pittsburgh Sleep Quality Index showed low scores throughout the 3-week study period (mean = 2.5 ± 1.3), indicating good sleep quality at home from week to week ($F_{2,10} = 0.52; P = .61$). During baseline and experimental nights, subjects slept between 11:30 PM (lights off) and 7:00 AM (lights on), fell asleep (ie, sleep latency) within normal range $^{23}$ (mean = 11 minutes ± 11.3), and showed no differences in sleep latency between experimental conditions ($F_{2,10} = 0.19; P = .83$).

Results showed a significant treatment effect for TST ($F_{2,9} = 4.84; P = .04$), which was lower during the morphine condition (mean = 342.8 minutes) compared to baseline (mean = 393.2 minutes; $P = .05$), although no differences were observed between morphine and placebo conditions (mean = 352.3 minutes; $P = .86$) (see Table 3). Nevertheless, results revealed a significant treatment effect for duration of SWS ($F_{2,9} = 19.63; P = .0005$), REM sleep ($F_{2,9} = 4.57; P = .04$), and NREM stage 2 ($F_{2,9} = 20.0; P = .0005$) (Figure 1). As predicted, there was a decrease in the mean percentage of SWS during morphine treatment nights (mean = 5.5%) compared to both baseline (mean = 19.8%; $P = .0005$), and placebo (mean = 16.8%; $P = .003$). In contrast to the 75% SWS decrease, there was an increase in mean percentage of NREM stage 2 following morphine (mean = 70.3%) compared to both baseline (mean = 53.6%; $P = .001$) and placebo conditions (mean = 55.1%; $P = .001$) (see Table 3).

As expected, the mean percentage of REM sleep was lower during morphine condition (mean = 15.6%) compared with baseline (mean = 20.9%; $P = .087$) and placebo (mean = 21.8%; $P = .046$). A treatment effect was also seen for the number of REM periods ($F_{2,9} = 8.8; P = .007$), revealing a small, yet significant, decrease during both morphine (mean = 3.6; $P = .019$) and placebo conditions (mean = 3.6; $P = .011$) compared with baseline (mean = 4.5). There was also a significant difference between treatment conditions in regard to REM density ($F_{2,9} = 25.5; P = .00001$), where the index of eye movements was significantly lower during morphine night (mean = 2.6) compared with both baseline (mean = 7.6; $P < .001$), and placebo (mean = 7.5; $P < .001$) (see Table 3).

Other sleep variables, such as EEG alpha-delta sleep, number of sleep-stage shifts, or correlates of arousal—including time awake, number of awakenings, and total number of EEG arousals—were similar across treatment conditions, as indicated in Table 3 (all $P > .05$). In fact, the index of both awakenings and total number of EEG arousals (ie, including those following movement, breathing events, or spontaneous) were in the normal range. $^{25,26}$ However, further detailed analyses revealed that, although the total number of EEG arousals were comparable throughout experimental conditions, there were significantly more spontaneous EEG arousals (index per hour) ($F_{2,9} = 5.9; P = .023$) during the morphine night (mean = 10.1) compared with both baseline (mean = 5.8; $P = .051$) and placebo (mean = 5.1; $P = .026$). Finally, there were no clinical effects of morphine or placebo on respiratory variables (Table 3).

Overall, subjective impressions of sleep quality during the baseline and experimental nights were related to objective EEG measures, though the subjective impressions of sleep duration, fragmentation, and quality did not differ significantly across treatment conditions (all $P > .05$). There were no apparent behavioral reactions to placebo and morphine injections prior to, or during, sleep. Also, there were no reports of anxiety during treatment or baseline nights, with the exception of 1 subject. This individual reported tachycardia following the first morphine injection, although seemed relaxed and went to sleep shortly thereafter. Still, this subject awakened 20 minutes after the second morphine injection with severe nausea. In fact, all subjects reported nausea as they got out of bed in the morning following morphine treatment, and all but 1 vomited. Protocols for the management of side effects were implemented during both placebo and morphine treatment conditions. Not all subjects asked or received IV administered doses of dimenhydrinate, but all were provided with oral doses to take as needed during the day.

DISCUSSION

The purpose of this study was to evaluate the effects of acute morphine administration on sleep in healthy young adults. It was found that clinical doses of morphine altered sleep architecture, as shown by reductions in SWS (75%) and REM (5%) sleep and by a 15% increase in NREM stage 2 sleep. Therefore the overall effect was a shift to lighter stages of sleep with no change in TST. Indeed, TST was diminished during morphine condition compared with baseline, but the difference between morphine and placebo conditions was in the order of 10 minutes and did not reach statistical significance. It is possible that both “injection” nights were perceived as more stressful than the baseline condition. Therefore, the lower TST in both experimental conditions suggests that the treatment effect per se was more consequential than the substance administered. Thus, reduced sleep time cannot solely be attributed to morphine. This possibility is further supported by other sleep measures, including sleep latency, wake after sleep onset, and sleep efficiency, being similar across experimental conditions.

Morphine decreased both the number of REM periods and the duration of REM sleep. Indeed, the mean percentage of REM-sleep duration was lower following morphine treatment, compared with placebo and baseline conditions. Still, REM sleep only
decreased by 5%, and the number of REM periods did not differ between morphine and placebo conditions. Again, the stressful effect of both treatment conditions on REM sleep is conceivable. In fact, it is generally found that during acute stress exposure, REM-sleep alterations are frequent, although no definitive conclusions can be drawn from the present results. However, the current data support alterations in REM sleep phasic activity, since eye movement density was significantly lower following morphine administration. Although mechanisms by which morphine alters REM sleep remain unknown, animal studies have shown that systemic morphine administration inhibits acetylcholine release in the pontine gigantocellular tegmental field. Cholinceptive neurons in this area are known to contribute to the generation of phasic events in REM sleep, including REM activity. These findings would explain, at least partially, the current decrease in phasic REM activity observed in our human subjects.

Though our results indicate that there were more spontaneous EEG arousals during morphine nights compared with baseline and placebo, the total number of EEG arousals and awakenings were in the normal range throughout treatment conditions for a population of young adults. These results differ from those of Kay and colleagues, who observed that the use of morphine increased arousal responses (ie, awakenings, EEG arousals) in their population of nondependent opiate-addict prisoners. It is unlikely that this discrepancy is due to lack of statistical power in the current study. Indeed, based on results from Kay and colleagues, for the number of awakenings (average = 20 ± 6), power analyses (power = 0.80; P = .05) revealed that 6 subjects would have been sufficient to detect a significant difference between experimental conditions in the present study. Hence, the current results would support the possibility that the previous report of increased arousal response following morphine was more likely due to the subject sample of nondependent opiate addicts presenting a differential arousal response to the drug. Further, the present results indicate that acute morphine administration prior to, and during, sleep does not increase the arousal response in healthy young adults.

As mentioned previously, providing effective analgesia is considered to be one of the most helpful interventions to reduce sleep disturbances in painful medical illness. Since morphine and other opioids remain the treatment of choice to relieve moderate to severe pain, it is imperative to understand their effects on sleep. Based on the results of this study, it seems that acute administration of clinical doses of morphine would alter sleep in ways similar to other types of medications such as sedative-hypnotics. Indeed, benzodiazepines, which are still commonly prescribed to treat insomnia, are potent suppressors of SWS and may also reduce REM sleep, although newer nonbenzodiazepine hypnotics (ie, zolpidem, zaleplon) do not produce such effects on sleep architecture. Further, even though morphine was administered in a range of doses similar to those used postoperatively, sleep disruptions observed in the present study appear to be less pronounced or qualitatively different from postoperative sleep patterns, which are characterized by severe reductions in TST and SWS, elimination of REM sleep, frequent awakenings, EEG arousals, and nocturnal movements (see Rosenberg-Adamsen et al for review). In addition, a recent study observed these postoperative sleep patterns in their patient population even when opioids were avoided. Still, further research is needed to correlate the present findings in patients with pain and also to directly compare the effects morphine with those of newer nonbenzodiazepine hypnotics and other analgesics on sleep structure of patients with pain.

Certain limitations of the present study need to be addressed. First, we evaluated sleep following the administration of a fixed dose of 0.1 mg/kg of morphine, and it is possible that larger doses of morphine would have brought dose-dependent sleep alterations, as implied in previous abstract publications. However, larger doses or repeated administration of morphine for dose-response trials would have been dangerous to perform with healthy volunteers without pain. Indeed, for the security and well-being of our subjects, it was decided, and agreed upon by the Institutional Ethics Committee, that morphine administration should not exceed this dose. Morphine dosage in the present study was chosen based on the results of an earlier study that showed that administration of 0.08 mg/kg in healthy subjects was effective in reducing sensory and affective responses to experimental nociceptive stimuli. Most importantly, morphine dosage and IV route of administration were chosen so as to be comparable to those used clinically for acute pain of moderate to severe intensity during the early phase of the postoperative period. All subjects reported adverse drug effects in the morning; therefore we believe the chosen dosage was sufficient to produce physiologic effects. However, this raises the possibility that the study’s blind condition was broken for the subjects. Most of them were nauseous and vomited in the morning when given morphine, while these reactions were not so notable during placebo or baseline conditions. Although serious, the effects of this possibility were counterbalanced in the study by the fact that the subjects were randomly assigned to each treatment condition, as presented in Table 2.

Other than abstract publications, this study is the first to report on the effects of clinically relevant doses of morphine on sleep in healthy pain-free young adults. Like earlier findings in animals, former opioid-dependent individuals, and postoperative patients, morphine was found to alter sleep structure by decreasing SWS. Unlike previous reports, however, its acute administration produced a moderate reduction in REM sleep and did not increase correlates of arousal. Further research is needed to correlate the present findings in patients with pain and to assess whether morphine can improve pain-disturbed sleep in these patients. Indeed, because there is increased awareness of an intimate relationship between pain and sleep, it remains essential to provide optimal pain relief to patients, which in turn may grant them a good night sleep.

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