Anesthesiology
69:327-331, 1988

# *Isoflurane Anesthesia Causes a Transient Alteration in Nocturnal Sleep*

C. A. Moote, M.D., F.R.C.P. (C.),* R. L. Knill, M.D., F.R.C.P. (C.)†

**Nocturnal sleep was studied in eight healthy young volunteers before and after isoflurane anesthesia. All night polysomnographic recordings were obtained for seven consecutive nights from approximately 2300 to 0700 h. On the morning after the third night each subject was anesthetized with isoflurane 1.1 MAC for approximately 3 h. The stages and indices of nocturnal sleep were calculated for each night of study according to standard criteria. The effects of anesthesia on nocturnal sleep were confined to the first postanesthetic night. Slow wave sleep (Stages 3 and 4) was moderately suppressed from 16 ± 1% to 6 ± 1%, and Stage 2 sleep reciprocally increased from 52 ± 2% to 60 ± 2% (mean ± SEM, $P < 0.05$). There were no detectable changes in the sleep onset latency, the total quantity of sleep, or the proportion of rapid eye movement (REM) sleep. Anesthesia was followed by daytime napping in six of the eight volunteers. Nocturnal sleep was similar in the subjects who napped and those who did not. It is concluded that anesthesia with isoflurane leads to a modest and a transient change in the architecture of nocturnal sleep. (Key words: Anesthesia: Recovery. Anesthetics, volatile: isoflurane. Sleep.)**

ABNORMAL SLEEP or sleep deprivation impairs both psychologic and physiologic well-being.[1]‡ Clinical observations suggest that sleep is commonly disturbed in the postoperative period.[2,3] For example, although regular hypnotic medication is required by only about 1% of the general population, it is routinely prescribed for 96% of surgical patients.[4,5] Polysomnographic studies, although limited, also indicate disordered sleep after surgery.[6,7] Following herniorrhaphy, the quality of nocturnal sleep appeared poor over the first two postoperative nights with frequent awakenings and reductions of both the rapid eye movement (REM) and slow wave stages of sleep.[6] After major thoracic procedures nocturnal sleep was found to be markedly disrupted, such that both REM and slow wave sleep were nearly abolished for several nights.[7] These severe alterations in sleep patterns could be important in the genesis of certain psychiatric and/or cardiorespiratory complications of the postoperative period.

Numerous factors might contribute to the genesis of disordered sleep after surgery including anesthesia, the surgical procedure, pain, distress, endocrine and metabolic responses to trauma, postoperative sedative/narcotic therapy, and environmental influences such as interruptions of sleep for nursing care. The role and relative importance of each of these factors is unclear. The purpose of this study was to assess the effect of anesthesia alone on nocturnal sleep over several nights. We exposed healthy volunteers to isoflurane 1.1 MAC anesthesia without a surgical procedure or its sequellae.

## Methods

The protocol was approved by the Health Sciences Standing Committee on Human Research at the University of Western Ontario and informed written consent was obtained. Eight healthy volunteers, three males and five females, 20 to 27 yr of age, were studied. All had been screened by an independent physician and judged to be fit for anesthesia. Each was within 10% of his or her ideal body weight, took no regular medication, and had no history to suggest a sleep-related disorder. For the duration of the study subjects were asked to refrain from daytime naps, to abstain from alcohol, and to avoid caffeine and excess fluid intake after 1800 h.

Each subject was monitored for seven consecutive nights while he or she slept in a quiet private hospital room adjacent to a monitoring facility. The first night was allowed for adaptation to the new sleep environment and monitoring equipment.[8] The second and third nights served as pre-anesthetic controls. Isoflurane anesthesia was administered on the morning of the fourth day, *i.e.*, on the morning following the third night of study.

Before the subject retired to bed each night oral temperature was measured. From "lights out" at approximately 2300 h until 0700 h the next morning, continuous polysomnographic recordings were made of the electroencephalogram (EEG), the electrooculogram (EOG) and the electromyogram (EMG). The EEG was obtained from scalp electrodes in the A1–C4 or A2–C3 position of the International 10–20 electrode system, the EOG from electrodes placed at the lateral canthus of each eye, and the EMG from electrodes placed in the

* Assistant Professor.
† Professor.
Received from the Department of Anesthesia, University Hospital and University of Western Ontario, London, Ontario, Canada. Accepted for publication April 1, 1988. Supported by Medical Research Council of Canada Grant MA6443.
Address reprint requests to Dr. Moote: Department of Anaesthesia, University Hospital, P.O. Box 5339, Postal Station A, London, Ontario, Canada N6A 5A5.
‡ Naitoh P, Pasnau R, Kollar EJ: Psychophysiological changes after prolonged deprivation of sleep. Biopsychiatry 3:309–320, 1971.

TABLE 1. Duration, Onset, and Efficiency of Sleep

| | Before Isoflurane (Control) | | After Isoflurane | | | |
|---|---|---|---|---|---|---|
| | Night 2 | Night 3 | Night 4 | Night 5 | Night 6 | Night 7 |
| Total sleep time (min) | 451 ± 7 | 442 ± 33 | 436 ± 12 | 410 ± 83 | 452 ± 26 | 446 ± 24 |
| Sleep onset latency (min) | 21 ± 3 | 15 ± 2 | 25 ± 2 | 24 ± 4 | 14 ± 3 | 21 ± 6 |
| Sleep efficiency (%) | 93 ± 1 | 92 ± 2 | 91 ± 2 | 85 ± 6 | 93 ± 2 | 93 ± 2 |
| Awakenings (no.) | 3 ± 1 | 6 ± 3 | 6 ± 2 | 5 ± 2 | 2 ± 1 | 2 ± 1 |
| Stage changes (no.) | 128 ± 10 | 125 ± 7 | 101 ± 9* | 126 ± 11 | 137 ± 13 | 130 ± 11 |

All values are given as mean ± SEM. Night I was the adaptation night.

* Significantly different from all other nights ($P < 0.05$).

submental area.§ Before the electrodes were placed the skin was superficially abraded to reduce its resistance to less than 10 kohms measured with an impedance meter (Grass® Model EZM5). Electrodes were silver/silver chloride and applied with a conductive electrolyte gel and either collodion or adhesive collars. The calibrated signals of all electrophysiologic variables were recorded on a Hewlett Packard® #7758B polygraph run at a paper speed of 10 $mm \cdot s^{-1}$.

Sleep stage¶ was determined for each 30-s interval of the night according to standard criteria. The records were scored with the interpreter unaware of the night of the study. The following variables of sleep were determined: 1) the total sleep time, *i.e.*, the total number of minutes asleep; 2) the sleep onset latency, *i.e.*, the number of minutes from lights out until the first epoch scored as Stage 2; 3) the sleep efficiency, *i.e.*, the total sleep time as a percentage of time in bed; 4) the number of awakenings during sleep; 5) the number of stage changes during the night; and 6) the time spent in individual stages of sleep, *i.e.*, Stage 1, Stage 2, slow wave sleep (Stages 3 and 4), and REM sleep, all expressed as a percentage of total sleep time.

On the morning of the fourth day, subjects remained fasting and were transferred to the Anesthesia Laboratory. An iv infusion of 5% dextrose and 0.2% normal saline was begun. Anesthesia was induced with isoflurane in oxygen (in one case supplemented with 50 mg iv of thiopental) and maintained with isoflurane. The trachea was intubated with a cuffed endotracheal tube. End-tidal concentrations of isoflurane were measured continuously using a Perkin-Elmer #1100 mass spectrometer (calibrated as described previously)[9] and kept at a near constant level equivalent to 1.1 MAC. Also monitored were the electrocardiogram, the arterial blood pressure (Riva-Rocci cuff), and the nasopharyngeal temperature. Arterial blood gas values were determined intermittently.

The period of anesthesia was 3 h, from about 0900 h to 1200 h. Normothermia was ensured throughout with a warming blanket and warmed iv fluids. The rate of iv infusion was adjusted to keep blood pressure within 20% of pre-anesthetic levels. No surgery was performed.

Following emergence subjects were watched closely and repeatedly requested to refrain from taking naps until recordings commenced later that night. The aim was to avoid the potential confounding effects of afternoon naps on nocturnal sleep.[10] Acetaminophen was made available to those who experienced postanesthetic headache or other discomfort.

Statistical assessment of sleep variables was by the ANOVA for repeated measures and the least significant difference test where indicated. The Student's *t* test was used to assess potential differences in sleep between the volunteers who received acetaminophen and those who did not. In all statistical tests a *P* value of less than 0.05 was considered significant.

## Results

The duration of anesthesia from induction to arousal was 182 ± 10 min (mean ± SEM). The values of arterial blood pressure, heart rate, nasopharyngeal temperature, and arterial blood gases during anesthesia were typical of healthy subjects anesthetized with isoflurane 1.1 MAC. As expected, all subjects were drowsy upon awakening from anesthesia. Despite our request, six of the eight could not refrain from sleep and napped intermittently over the subsequent 2–6 h. Individual naps were limited to 20 min in duration, by arousing the subject if required. Five subjects complained of mild

§ Rechtschaffen A, Kales A: A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Los Angeles, BIS/BRI, UCLA, 1977.

¶ Wakefulness merges into sleep along a continuum that has been divided into stages numbered according to their increasing depth. After wakefulness is drowsiness, Stage 1. True sleep begins with Stage 2; deeper yet are Stages 3 and 4, which together are called slow wave sleep. Dreaming occurs during rapid eye movement (REM) sleep.

TABLE 2. Time Spent in Individual Stages of Sleep

| | Before Isoflurane (Control) | | After Isoflurane | | | |
|---|---|---|---|---|---|---|
| | Night 2 | Night 3 | Night 4 | Night 5 | Night 6 | Night 7 |
| Stage 1 (%) | 6 ± 1 | 7 ± 1 | 10 ± 2 | 9 ± 2 | 9 ± 2 | 8 ± 1 |
| Stage 2 (%) | 51 ± 1 | 52 ± 2 | 60 ± 2* | 50 ± 2 | 48 ± 3 | 49 ± 1 |
| Slow wave (%) | 16 ± 2 | 16 ± 1 | 6 ± 1* | 17 ± 3 | 16 ± 2 | 16 ± 2 |
| REM (%) | 26 ± 2 | 24 ± 2 | 22 ± 2 | 24 ± 3 | 25 ± 3 | 26 ± 1 |

All values are given as mean ± SEM.
* Significantly different from all other nights ($P < 0.05$).

headache following anesthesia and received acetaminophen 325 mg once.

The variables of sleep on both control nights were stable and within the range of normal values for healthy young adults (tables 1 and 2, nights 2 and 3).[11] Isoflurane anesthesia did not detectably affect the total sleep time, the sleep onset latency, the sleep efficiency, the number of awakenings during sleep, or the percentages of Stage 1 and REM sleep on any postanesthetic night (tables 1 and 2, nights 4–7). However, anesthesia did reduce the amount of slow wave sleep and increased Stage 2 sleep on the night immediately following anesthesia (table 2, night 4). Individual periods of Stage 2 were somewhat longer in duration, thereby decreasing the number of stage changes (table 1, night 4). These effects on sleep architecture appeared predominantly in the first half of the night. They were similar in the six subjects who had had postanesthetic naps and in the two who had not. There were no detectable changes in either slow wave or Stage 2 sleep during the subsequent postanesthetic nights.

Bedtime temperature increased slightly from 36.8 ± 0.2° C on the control nights to 37.3 ± 0.1° C (mean ± SEM) on the night of anesthesia ($P < 0.05$). The administration of acetaminophen in five subjects did not modify this temperature elevation, nor did it affect the changes in slow wave and Stage 2 sleep.

## Discussion

Isoflurane 1.1 MAC anesthesia for 3 h did not affect the time to onset of sleep, nor the time spent sleeping on any night after anesthesia (table 1), suggesting that it did not supplant the normal requirement for nocturnal sleep. However, there was a slight change in the architecture of sleep wherein the proportion of slow wave sleep was reduced in the night immediately following anesthesia (table 2). This loss of slow wave sleep was evident primarily in the first half of the night, that portion of the night in which the majority of slow wave sleep normally appears.[11] It was replaced with a reciprocal increase in Stage 2 sleep, as has been observed in other conditions of limited slow wave sleep.[6,10,12] There were no associated changes in Stage 1 or REM sleep. Such a selective curtailment of slow wave sleep has been considered by some to represent a reduction of the overall soundness of sleep.[6] Thus, although anesthesia did not affect the total quantity of sleep, it may have transiently lessened its quality.

We are aware of no other studies of nocturnal sleep following inhalational anesthesia alone in humans. In cats given halothane 0.5–1.5% inspired for 5 h, the proportion of slow wave sleep increased for one or two nights, REM sleep was absent for three or four nights, and sleep structure remained disturbed for a week.[13] To what extent these markedly different findings relate to species, anesthetic agent, or other factors is not clear.

How can one account for this moderate disturbance of sleep in the night following isoflurane anesthesia? The anesthetic experience of our subjects included several factors that might have affected sleep either individually or in combination, *e.g.*, isoflurane, fasting, temperature elevation, napping, and anesthesia-related loss of wakefulness and activity. Although this study was not designed specifically to address the potential role of any of these factors, certain reasonable inferences can be made.

The first factor to be considered is a direct effect of isoflurane persisting into the first postanesthetic night. A wide variety of CNS depressants including the barbiturates, the benzodiazepines, the phenothiazines, meprobamate, glutethimide, and ethanol have been found to alter the architecture of nocturnal sleep if taken at bedtime in a dose adequate to produce sedation.[14,15] Isoflurane is also a CNS-depressant. The dose remaining in our subjects at bedtime is not known but can be estimated to have been less than 0.01 MAC,[16] a dose well below that which would normally produce sedation. Such a tiny amount of isoflurane is unlikely to have affected sleep in a substantive way unless its actions on sleep are far more potent than those of other CNS depressants.

In addition, the particular changes in sleep we observed were clearly different from those that have been

found with all other CNS depressants tested.[14,15] The primary effect of these agents is to reduce the proportion of REM sleep. Some that reduce REM sleep also decrease slow wave sleep. However, to our knowledge, no CNS depressant suppresses slow wave sleep without affecting REM sleep, as was observed in the night following administration of isoflurane (table 2). Thus, the changes in postanesthetic sleep cannot be ascribed to the direct effects of the anesthetic agent itself.

Another pharmacologic factor that may have altered sleep in the subjects is the acetaminophen, which was taken by five of the eight subjects on the night of anesthesia. Although the specific effects of acetaminophen on sleep are unknown, a survey of subjective impressions suggests that it actually improves the quality of sleep.[17] In the postanesthetic subjects the quality of sleep, as reflected by the proportion of slow wave sleep, was poorer not better (table 2). Furthermore, there were no detectable differences in the sleep of the subjects who received acetaminophen and those who did not. Thus, it is unlikely that acetaminophen was responsible for the changes in sleep we observed.

Other potential causes of the altered sleep following anesthesia relate to certain physiologic changes associated with the state of anesthesia or its administration.

Fasting is an accompaniment of anesthesia, which has the potential to disturb sleep.[18] All of the subjects ingested food until midnight prior to the study and then fasted until 0830 h. At that time an iv infusion of 5% dextrose in 0.2% sodium chloride was established and at least 1 l infused during the course of anesthesia. After the initial recovery from anesthesia at about 1300 h, each subject ingested juice and by later that afternoon ate a normal meal. Previous observations indicate that such a brief interruption of food and caloric intake would not affect nocturnal sleep. For fasting or starvation to have even minimal effects on sleep, it must be maintained for at least 24 h and to alter slow wave sleep, be extended to at least 48 h.[18] Furthermore, the effect on slow wave sleep is to increase it[18] rather than reduce it, as was observed (table 2). We conclude that fasting did not cause the changes in sleep after anesthesia.

The temperature of our subjects increased slightly (approximately 0.5° C) and consistently on the night of anesthesia.** It has been observed that a somewhat greater elevation in temperature (approximately 1.0° C) induced by pyrogen administration in humans causes a substantial reduction in slow wave sleep together with an equally marked decrease in REM sleep and a greater number of awakenings.[19] Anesthesia in our subjects resulted in a reduction of slow wave sleep but no detectable change in REM sleep or the number of awakenings (tables 1 and 2). Thus, unless there are different temperature thresholds for the effects of fever on slow wave sleep, REM sleep, and awakenings, the elevated temperature of our subjects does not explain their postanesthetic sleep.

Another factor that may have altered nocturnal sleep after anesthesia was the intermittent napping during the afternoon recovery period. Ordinary afternoon naps, which are more or less miniatures of nocturnal sleep,[20] can modify subsequent nocturnal sleep by reducing the slow wave sleep component.[10] Postanesthetic naps could conceivably do the same. However, several pieces of evidence suggest that the naps of our subjects were not the principal cause of the changes in nocturnal sleep we observed. First, the effects on nocturnal sleep were similar in the six subjects who experienced naps and in the two who did not. Second, ordinary naps that cause a moderate reduction in nocturnal slow wave sleep do so only if they themselves include a substantial amount of slow wave sleep.[10] Although we did not monitor the naps in our subjects, we doubt that they incorporated any slow wave sleep. These naps were nearly always interrupted before 20 min had elapsed, and this is the minimum period of latency necessary for the development of slow wave sleep.[11,20] Furthermore, even uninterrupted naps following anesthesia and surgery have been found to be devoid of slow wave sleep.[21],†† Third, even if this inference is incorrect and the postanesthetic naps of our subjects did include a considerable amount of slow wave sleep, the effect of such naps would explain only a portion of the reduction of nighttime slow wave sleep that was observed. Daytime naps that are laden with slow wave sleep diminish nocturnal slow wave sleep by only 30%,[10] whereas anesthesia in our subjects reduced slow wave sleep by more than 60% (table 2). Although we cannot rule out the possibility that postanesthetic napping played a contributing role in altering postanesthetic nocturnal sleep, we doubt it was the only or major factor.

The suspension of wakefulness and activity associated with anesthesia offers another explanation for the alterations in sleep observed. Studies of awake/activity/sleep patterns that have been altered in a variety of ways indicate that the amount of nocturnal slow wave sleep relates directly to the duration of wakefulness before sleep and/or the level of muscular or metabolic activity

** The reason for this temperature elevation is unclear. It may have been due to the cumulative effects of the minor trauma associated with placement of the iv catheter, arterial punctures, and endotracheal intubation.

†† Knill RL, Moote CA, Skinner MI, Rose EA, Lim G: The early post anaesthetic state is primarily light and fragmented NREM sleep. (Unpublished observation)

during wakefulness before sleep.[12,22-25] Thus, if the awake period is extended for several hours or the level of activity is greatly augmented (as with intense exercise or hyperthyroidism), the amount of subsequent nocturnal slow wave sleep increases more or less in parallel with the added wakefulness or activity.[22-25];‡‡ Alternatively, if activity is restricted (as with quadriplegia), the amount of deep slow wave sleep appears reduced.[12] This apparent linkage of slow wave sleep to prior wakefulness and activity may reflect the provision of wakefulness/activity recovery functions during slow wave sleep.[25]

If nocturnal slow wave sleep continues to be as responsive to prior wakefulness and activity in the context of anesthesia, then the abolition of wakefulness together with the suppression of muscular and metabolic activity for 3 h of anesthesia would readily explain the reduction of slow wave sleep we observed.[22] The relatively brief interruptions of wakefulness and activity associated with the postanesthetic naps of our subjects would not be expected to have an important effect unless these interruptions included substantial amounts of slow wave sleep (as discussed above).

The compatibility of the wakefulness/activity factor with the particular changes in sleep we observed, together with the lack of evidence to support a primary role for any other factor, leads us to favor loss of wakefulness/activity as the best single explanation for the altered architecture of sleep after isoflurane anesthesia. It must be emphasized, however, that we have no direct evidence to prove this interpretation or refute others.

Anesthesia together with major surgery can result in a severe disruption of nocturnal sleep, with marked suppression of both REM and slow wave components of sleep for several nights.[7] The major finding of the present study is that isoflurane anesthesia without surgery produces changes that are somewhat different and comparatively brief and modest. This suggests that anesthesia with this agent would play at most a minor role in the overall disturbance of postoperative sleep.

The authors wish to thank the volunteers who participated in the study, J. Clement who helped with the performance of the study, and L. Nolan who assisted in the preparation of the manuscript.

‡‡ Oswald I, Dunleavy DLF, Strong JA: Hyperthyroidism and the sleeping brain. Hormones 3:278, 1972.

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